MODERN TRENDS

IN

DERMATOLOGY

(SECOND SERIES)

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Edited by

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MODERN TRENDS SERIES

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INTRODUCTION

Five years ago the first volume of *Modern Trends in Dermatology* was published. The Editor desires at the outset to thank the twenty-three eminent contributors to that work because they set such a high standard that it has not been difficult to persuade twenty-two equally distinguished colleagues to undertake the labour of contributing to the second series. The word "labour" is used advisedly for it is no light task to write a chapter for a book such as this not only have the contributors to cull the material from journals and other sources, and—having assimilated it—present the data with critical appraisement, but they have to add the lustre of their own reflections and maybe speculate on future developments. Much care, time and thought have had to be spent on each section, and the Editor hopes that those who have wrestled with the problems and contributed to the present volume will accept his thanks.

Except for the chapters on cutaneous tuberculosis, sarcoidosis and leprosy the reader will not find any easy gradation of subjects, and he will be well advised to read each chapter separately and not attempt to read the book in a few sittings. Professor Leslie Banks has set the background of our endeavours by depicting what has happened in Great Britain in previous centuries so far as Europe is concerned parallels to his observations must exist in many countries his work further emphasises the truth of the statement attributed to Pierre Charron (1541–1603) *la vraie science et le vrai étude de l'homme c'est l'homme*" and is inserted at the beginning of the book to remind the reader that however important the details considered later may be, most of us must eventually return not only to the problems encountered in the clinic and at the bedside, but also to the wider problems concerning the adaptation of man to his environment and the prevention of disease. Dr I. Macalpine's chapter on psychiatry would seem best placed after this essay and thereafter we turn to anatomy physiology and functional pathology studies of certain problems and various diseases, and, finally to treatment.

The reader is urged not to regard the placing of chapters in the book as a measure of their significance each is complete in itself and its place is only determined by the effort to make a unity of a very diverse accumulation of contributions.

I wish gratefully to acknowledge my indebtedness to the following persons Dr H W Barber for advice concerning certain matters in the planning of the book Dr W E. de B Diamond for information concerning plastics Miss E. M L. Finch for secretarial assistance Professor L. P Garrod, for advice concerning bacteriology Mr N K. Harrison for an intricate drawing and for certain photographs from the Photographic Department of St. Bartholomew's Hospital Dr A M Kligman for his generosity in allowing unpublished work and photographs to be used in the chapter on mycology Dr Claude Lillingstone of Sunnfjord for the translation of Professor Danbolt's chapter Miss W Tatham Thompson for the translation of the chapter written by Drs. A. Tzanck and O R. Melki Dr V R. Wheatley for the proof reading of certain sections and for advice concerning chemistry finally to the members of the Medical Department of Messrs. Butterworths whose expert advice and assistance have been invaluable.

London October 1953

R. M B MacKenna

CHAPTER 1

ECOLOGY IN RELATION TO DERMATOLOGY

A. Leslie Banks

About the year 1780 Plenck, a professor at the University of Budapest, published his classification of skin diseases, based mainly on the anatomical character of the eruption, and divided into fourteen classes. The industrial revolution had already begun, but it is not unreasonable to assume that the pattern of disease was, as yet, little influenced by the rhythm of the new machines. Some indication of the coming changes may be gleaned from the classification introduced a few years later by Robert Willan, in which, although he followed Plenck closely, he reduced the number of orders to eight, based on elementary lesions, and omitted the order Crustae in favour of Exanthemata. During his relatively short life (he died in 1812 at the age of 55 years) Willan was able to publish also his study of occupational skin diseases and by the time Jean-Louis Alibert was making his abortive attempts to classify skin diseases according to their natural relationship the industrialization of Europe was in full swing.

In 1844 Hebra introduced his system of classification of skin diseases based chiefly on morbid anatomy and his twelve classes were almost universally adopted. They were (1) hyperaemic affections of the skin (2) anaemic affections of the skin (3) morbid conditions of the secretions of the cutaneous glands (4) exudations (5) haemorrhages (6) hypertrophies (7) atrophies (8) innocent growths (9) malignant growths (10) ulcers (11) neuroses (12) parasites.

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THE SOCIAL BACKGROUND

The introduction of malignant growths and neuroses by Hebra strikes a modern note, but he, and those who followed him, were handicapped by lack of knowledge of the causes of the diseases with which they were confronted. That criticism no longer applies generally today but current dermatological thought may be equally handicapped by the confused and changing environment of the patient. The social background has altered markedly over the past 200 years, and changes are still going on. The future pattern of disease generally and of disease as

and conditions of work, for man, woman, and child alike, were to lay the foundations of ill-health for the next 200 years.

The 19th century

It is surprising to find that, in spite of Malthus' gloomy prognostications in 1798 the population increase at the beginning of the 19th century was of the order of 10 per cent in 10 years, and between 1801 and 1901 the number of people in Great Britain increased three and a half times. Even so the expectation of life remained low. In 1838 a gentleman in London might expect to live for 44 years from birth, a tradesman 26 years, and a labourer 24 years.

It may not be inappropriate to enquire at this point into the type of person produced by the industrial revolution, and the conditions under which he lived. As to the latter the reports of the first medical officer of health to the City of London leave no doubt. In his first report, Simon (1849) wrote.

> "It is too true that there are swarms of men and women who have yet to learn that human beings should dwell differently from cattle swarms, to whom personal cleanliness is utterly unknown swarms, by whom delicacy and decency in their social relations are quite unconceived. Men and women, boys and girls, in scores of each using jointly one single common privy grown persons of both sexes sleeping in common with their married parents a woman suffering travail in the midst of the males and females of several families of fellow lodgers in a single room an adult son sharing his mother's bed during her confinement—such are instances recently within my knowledge (and I might easily adduce others) of the degree and of the manner in which a people may relapse into the habits of savage life, when their domestic comfort is neglected, and when they are suffered to habituate themselves to the uttermost depths of physical obscenity and degradation.

Simon's second report is even more to the point, for on the 26th November 1850 he wrote.

> "This is evil enough but worse remains behind. *It is* no uncommon thing, in a room of 12 feet square or less, to find three or four families *styed* together (perhaps with infectious disease among them), filling the same space night and day—men, women, and children, in the promiscuous intimacy of cattle. Of these inmates it is nearly superfluous to observe, that in all offices of nature they are gregarious and public that every instinct of personal or sexual decency *is* stifled that every nakedness of life is uncovered there. Such an apartment is commonly hired in the first instance by a single pair who sub-let a participation in the shelter probably to as many others as apply Sometimes noxious occupation is carried on within the space thus, I have seen mudlarks (*chiffoniers*) sitting on the floor with baskets of filth before them, sorting out the occasional bits of coal or bone, from a heterogeneous collection made along the bed of the river or in the mouths of the sewers and this in a small room, inhabited night and day by such a population as I have described. I purposely refrain from any attempt to illustrate all the horrors which are incidental to this method of life but, as a single exemplification of the text (chosen not because of its rarity but because it happens to occur at the moment) I insert an extract from a note, with which I was favoured a fortnight ago, by Mr Hutchenson, Surgeon to the North District of the West London Union 'I was sent for to attend a poor Irish woman in labour at half-past six o clock yesterday morning, at 17 Fox and Knot Court. There were three families, each consisting of a man and wife and two or more children, in a small room, 15 feet by 8 all lying upon dirty rags on the floor I found one of the children suffering under small-pox. The adjoining room was occupied by six grown-up persons and

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In order to attempt to justify such a statement it is necessary to return to the time when the first indications of change appeared. For this purpose Great Britain affords a useful example, for it was in these islands that the industrial revolution first began, and here it reached its maximum effect.

The 16th and 17th centuries

When William Harvey published his discovery of the circulation of the blood in 1628 the population of Great Britain numbered about six million people. In spite of a high birth rate the increase in population was slow for less than half the children born survived to adult life, and it is doubtful whether the expectation of life from birth exceeded 19 years in this, or in the succeeding century. The pattern of disease was still in fact mediaeval. Plague and famine toured Europe at intervals on the grand scale, and smallpox, malaria, typhus dysentery and the other acute infections, followed their own unhindered rhythm, and made life short and insecure. Civil war drove people to the towns almost as frequently as pestilence sent them to the country. The housing of the poor had been notorious even in Elizabethan times, and the diarists, and especially Evelyn, bore eloquent testimony to the faulty sanitation whose memorial persists in such street names as Foul Lane and Laystall Street. Personal cleanliness had if anything, declined since the Middle Ages, for the public baths had acquired an evil reputation and had become unfashionable. It is doubtful if the example of Queen Elizabeth I who had taken a bath once a month to encourage others whether she needed it or not, was widely followed even by the wealthy. It is not unfair to assume that sepsis, parasitic infections, and the exanthemas dominated the pattern of skin disease, and established a hold on the mass of the population that is only now being loosened.

The 18th century

In the 18th century the general death rate began to fall and the population increased by 50 per cent. Even so the picture is not a pretty one. The prevalence of ignorance, poverty drunkenness and promiscuity are well shown in Hogarth's drawings, and in Boswell's *London Journal*. It is true that plague had paid its last major visit to this island, and that small-pox was beginning to respond to the practice of inoculation introduced from Turkey by Lady Mary Wortley Montague early in the century. In their place came syphilis and tuberculosis as the great destroyers of life and *inter alia* as causes of diseases of the skin. Life was still terribly brief and it has been estimated that between 1730 and 1749 3 out of every 4 children in London died before reaching the age of 5 years (Sand 1952). Daniel Defoe had noted in his *Tour Thro' the Whole Island of Great Britain* in 1724–26 that children in the woollen industries of Yorkshire were set to work from the age of 4 years but the economy of the country was still primarily a domestic one, with the home serving also as the workplace. Then came a sudden and dramatic change. In the second half of the 18th century the rhythm of the machine began to succeed that of the human body and the factory took the place of home work. The results are well known. The rush to the towns and the desertion of the countryside the appalling slums the poverty and malnutrition, and the dreadful hours

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two children In the circumstances to which my Report refers, scenes of this description must of necessity be *habitual* and it is to their habit, not to their exceptional occurrence, that my remarks apply —J.S."

At this time also the Registrar-General (1850) was seeking for a simple yardstick whereby to measure the degree of literacy of the population. He decided that those who could write would sign the marriage register and only make their mark if they could not do so He found that

"It is probable that the mark is only resorted to where the parties are unable to write their names, or where they write imperfectly This simple test affords, therefore, a good indication of the diffusion and progress of elementary education among the people. Now in 1850 of 100 men that married 68·9 wrote their names and of 100 women 53 8 wrote their names and 31 1 of the men and 46 2 of the women signed the marriage register with marks" The Registrar-General concluded that "It is a striking example of the neglect of elementary education in England that at the time these people were educated 46 in every hundred of the future mothers of the English population cannot write. How long is the population to remain in this state of *ignorance?*"

To complete the picture turn now to William Farr s annual letter to the Registrar General on the causes of death in England (Farr 1852) In that year which was a prosperous one, with the price of provisions low until after harvest, when the price of wheat rose, and potatoes, which are consumed so largely by people of all classes and ages, became dear" scarlatina caused 18,887 deaths, diarrhoea 17 617 deaths, typhus, smallpox and cholera numbered their victims in thousands and so did measles and whooping-cough Above all there was consumption the greatest the most constant, and the most dreadful of the diseases that affect mankind It is the cause of nearly half the deaths that happen between the ages of 15 and 35 years.

References to the dangers of maternal ignorance and neglect recur again and again. In 1861 an enquiry into the "*Excessive Mortality of Infants in some Manufacturing Places*" (Simon, 1861) revealed certain large towns where women were greatly engaged in branches of industry away from home and where consequently the home is ill kept where the children are little looked after and where infants who should be at the breast are improperly fed or starved, or have their cries of hunger and distress quieted by those various fatal opiates which are in such request at the centres of our manufacturing industry Two years later the results of another inquiry were published (Simon 1863) and showed that even in entirely rural districts the habitual mortality of young children was almost as great as in the worst factory towns, Wisbech in Cambridgeshire, being almost as bad in this respect as Manchester The damaging factor was again the employment of adult women. The mother as soon as she could rise from her confinement, went to work leaving the infant to anyone who would pretend to take care of it It was more than once related that women who had lost two or three successive children lost no more after it had been plainly signified to them that their proceedings were watched "

Such was the position in town and country less than one hundred years ago and we may surmise that the pattern of disease of the skin, like the pattern of disease in general, reflected the almost universal squalor poverty ignorance and indifference

with the addition, in the manufacturing areas, of conditions directly attributable to industrial poisoning.

A STATISTICAL NOSOLOGY

Unfortunately it is only possible to generalize, for morbidity studies were non-existent and death rates misleading. William Farr wrote his first annual "letter" to the Registrar-General on the 6th May 1839. In it he stressed the advantages of a Statistical Nosology and under the heading of diseases of the integumentary system he included carbuncle phlegmon, whitlow ulcer fistula, disease of the skin, leprosy purpura, *Noli me tangere* (that is malignant forms of ulceration, including rodent ulcer), pompholyx, impetigo, scald head and elephantiasis. He commented that "in a topographical arrangement, smallpox, measles scarlatina, and erysipelas, should be added to disease of the integumentary system. In that case the mortality would be 1·976 per 1,000" (Farr 1839). Unlike diseases of the nervous system and respiratory organs, he found little difference between town and country in the death rate from diseases of the skin. If confirmation is needed of the appalling conditions in the heart of English cities at that time it may be found in the computation of Farr that the greatest density attained was nearly 243 000 inhabitants to a geographical square mile. It was against this background that Chadwick reported to the Government on the effects of damp, filth and over crowding in causing or aggravating epidemic and other disease among the labouring classes (Chadwick, 1842).

In the Registrar-General's twentieth annual report Farr takes occasion to remark that "diseases of the integumentary system are less common than they were in the middle ages, when England was covered with hospitals for lepers. The people, however still neglect the skin and its excretions frequently absorbed, undoubtedly give rise to some forms of zymotic disease. The shower bath with warm, tepid, or cold water according to circumstances, is not used by people who wash their hands and faces every day more than once (Farr 1857). It is clear that the lessons contained in Erasmus Wilson's popular treatise on the skin and hair had not yet borne fruit (Wilson 1845). Indeed it is difficult to see how a healthy skin could be maintained in the absence of facilities for cleanliness and well-being.

By 1875 Farr was able to report the beginnings of a permanent change in the incidence of disease. He noted that phthisis had declined in the past twenty-five years, but that cancer was growing more common and fatal. Included under this latter heading were eleven deaths due to sweep's cancer and seventy-eight deaths from lupus (Farr 1875). At last the intensive efforts of the reformers were beginning to bear fruit. Under the triple spurs of compassion, the fear of cholera, and the common-sense realization of the folly of letting skilled workers die prematurely much had been achieved, and from the eighteen-seventies can be traced the modern trends. It is customary to attribute much to the Public Health Act of 1875 and the results of this great statute must not be minimized, but other factors came into operation about that time also. Compulsory education did more than educate the children it removed one of the incentives for having a large family for children could no longer be set to work from the age of four years. It also provided an outlet for the educated woman, who, as teacher was able to influence the mother as well as the child. From this time also many women sought occupation

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"It is probable that the mark is only resorted to where the parties are unable to write their names, or where they write imperfectly This simple test affords, therefore, a good indication of the diffusion and progress of elementary education among the people. Now in 1850 of 100 men that married 68·9 wrote their names and of 100 women 53 8 wrote their names and 31 1 of the men and 46 2 of the women signed the marriage register with marks." The Registrar-General concluded that It is a striking example of the neglect of elementary education in England that at the time these people were educated 46 in every hundred of the future mothers of the English population cannot write. How long is the population to remain in this state of ignorance?"

To complete the picture turn now to William Farr s annual letter to the Registrar General on the causes of death in England (Farr 1852) In that year which was a prosperous one, with the price of provisions low until after harvest, when the price of wheat rose, and potatoes, which are consumed so largely by people of all classes and ages, became dear" scarlatina caused 18 887 deaths, diarrhoea 17 617 deaths, typhus, smallpox and cholera numbered their victims in thousands and so did measles and whooping-cough Above all there was consumption "the greatest, the most constant and the most dreadful of the diseases that affect mankind. It is the cause of nearly half the deaths that happen between the ages of 15 and 35 years.

References to the dangers of maternal ignorance and neglect recur again and again In 1861 an enquiry into the *Excessive Mortality of Infants in some Manufacturing Places*" (Simon, 1861) revealed certain large towns where women were greatly engaged in branches of industry away from home and where, consequently the home is ill kept where the children are little looked after and where infants who should be at the breast are improperly fed or starved or have their cries of hunger and distress quieted by those various fatal opiates which are in such request at the centres of our manufacturing industry" Two years later the results of another inquiry were published (Simon 1863) and showed that even in entirely rural districts the habitual mortality of young children was almost as great as in the worst factory towns, Wisbech, in Cambridgeshire, being almost as bad in this respect as Manchester The damaging factor was again the employment of adult women The mother as soon as she could rise from her confinement went to work leaving the infant to anyone who would pretend to take care of it. It was more than once related that women who had lost two or three successive children lost no more after it had been plainly signified to them that their proceedings were watched

Such was the position in town and country less than one hundred years ago and we may surmise that the pattern of disease of the skin, like the pattern of disease in general, reflected the almost universal squalor poverty ignorance and indifference

were too hungry to learn. The value of the early work of the school medical service, in detecting and treating disease, including abnormalities of the skin, and in teaching the elementary rules of cleanliness, is beyond dispute, and it is worth remembering that the children so taught are the parents of today. Equally important has been the provision of school meals and milk, and it is not too fanciful to suggest that one of the results of improving the nutrition of schoolgirls and expectant mothers may be a reduction in some of the diseases due to prenatal influence.

In 1911 came the first National Health Insurance Act, with the State committed irrevocably to a share in responsibility for personal health and welfare. Henceforward public funds were to be devoted to the improvement in health of the individual, in addition to ensuring a sanitary environment. The 1911 Act made possible great extensions in the care of tuberculosis, but these, and the influence of the new panel doctors, were hardly operative before the outbreak of the First World War. The major health events of that war are well known. The attack on the venereal diseases and tuberculosis, the intensification of care for mother and child, and the advances in surgery, radiology and bacteriology are all on record. Less obvious but equally important was the effect of subjecting millions of men, for the first time in history, to regular medical inspection, communal life, and compulsory cleansing and disinfestation. When the war ended long and earnest discussions were held on the advisability of a health service for the nation, but the Ministry of Health, established in 1919, was content to concentrate on the well tried methods of prevention of disease and to leave clinical medicine alone. Even so the progress made in both fields was remarkable. Diabetes and pernicious anaemia were early brought under control, infant mortality declined steadily, the health of industrial workers was improved, and the killing power of the great infections was reduced.

Slow but steady progress towards the co-ordination of medical services was being made when the Second World War broke out in 1939. On this occasion it was clear that the luxury of inertia could not be afforded. An emergency medical service sprang into being on a national basis, and nearly every member of society became eligible for medical care in one way or another. The evacuation of millions of children from towns to country brought to light an unpleasantly high proportion of parasitic infestations of the skin, and revealed the presence of many psychological and emotional problems of childhood.

It is difficult even now to measure the effects of all the advances made since 1939. Perhaps the most outstanding is the discovery and use of the antibiotics, but, taking the world as a whole, the effects of DDT and the other insecticides, have been equally dramatic in changing the pattern of disease. Nor must the results of improved nutrition, especially of expectant mothers, be overlooked, for recent experimental work shows that deprivation early in pregnancy may possibly be as disastrous as virus infections in the production of congenital abnormalities (Warkany 1949). The advances in surgery, blood transfusion and laboratory techniques are well known, and the ground was ready for an extension of the use of radioactive isotopes, both for diagnosis and treatment. Nor was the opportunity for research into the causes of diseases of the skin neglected, for unlike the First World War, skin eruptions were no longer popularly associated with venereal disease in the military mind.

in nursing and allied fields, and it is significant that the birth rate in Britain began to decline from the year 1870 long before the practice of contraception became general The social circumstances of all classes also began to improve There had been no widespread famine in Europe since 1817 or in the British Isles since the potato famine of 1847 Hours of work were being reduced and women were prohibited from employment in some industries. By the nineties it began to appear as if all was for the best, and that the country was at last recovering from the excesses of the industrial revolution The expectation of life from birth had risen to 44 years for a boy and 48 years for a girl, and the general death rate had declined It is true that nearly four women died in childbirth for every 1 000 births that typhoid, diphtheria, measles, and whooping-cough numbered their victims in thousands and that most houses in the country lacked fixed baths but the tempo of life was still that of the horse-drawn vehicle and the steam engine, and war and famine at least had gone. Even so in the field of dermatology Robert Liveing could already write that "Lastly some forms of skin diseases, such as gutta rosea (probably rosacea) and many kinds of eczema are aggravated and perpetuated if not produced, by indigestion, want of rest, and mental troubles and anxieties therefore suitable diet, rest, and change of air and of surroundings, will not be without their influence in effecting a lasting cure" (Liveing, 1894)

It was not long before the whole nation was disturbed by want of rest, by mental troubles and anxieties. Curiously enough, as it seems now it was not the discovery of the petrol engine or the advances of the physicists, which disturbed the last years of the nineteenth century but a small "colonial" war To be trounced by the Boers was disturbing enough but it was the revelation of the harvest of physical unfitness, now to be reaped, which shook the complacency of the nation. Rejections of recruits coming forward to fight for the Queen varied between 40 per cent and 60 per cent. Such a pointer to the health of the community in a highly competitive world could not be ignored The Inter-departmental Committee on Physical Deterioration, established in 1903 reported in the following year and from its fifty three recommendations sprang, directly or indirectly much of the health and welfare legislation of the present day The next fifty years were to witness a revolution in the prevention, diagnosis, prognosis and treatment of disease In those changes diseases of the skin have shared to the full

As a result of industrialization, with all its attendant evils, the eighteenth century pattern of disease, still to be seen today in many parts of the world, had been accentuated. Sepsis, parasitic infestations—both major and minor—the acute infectious fevers, syphilis and tuberculosis, all flourished in the crowded towns and cities. To these the process of industrialization had added its own contribution of malnutrition, deficiency diseases, and physical and chemical causes of disease of the skin The results may be seen at a glance by anyone who chooses to turn over the leaves of the text books of the day Plate after plate beautifully drawn and coloured, show the extremes to which the human skin can react Small wonder that diagnosis was often difficult, with such a plethora of lesions from which to select.

One of the earliest recommendations of the Inter-departmental Committee to be implemented was the establishment of a school medical service in 1907 It is interesting to note that it was necessary first (in 1906) to arrange for the provision of school meals, for it had been found that about 10 per cent of schoolchildren

Control of Infection

With these population changes there have been remarkable alterations in the pattern of disease. Septic infections, so many of which arise first in the skin before manifesting themselves more deeply in the body are now controllable by the antibiotics. Osteomyelitis, and other acute infections of bones and joints, including the mastoid process no longer pose the major problems of twenty-five years ago, with their demands for heroic surgery painful dressings, and prolonged stay in hospital. "Malignant" endocarditis, and subacute bacterial endocarditis, have now taken second place to degenerative disease of the cardiovascular system, and pyaemia and septicaemia no longer have their former ominous meaning. It is interesting to speculate on the extent to which these changes are due to the progress of health education over the past forty years. Certainly increased cleanliness of the skin, together with more healthy conditions of the upper respiratory passages, have played a prominent part. The decline in casual labour in favour of steady employment, and with it the growth of self-respect of the family have also been important in reducing drunkenness and brutality and in raising the level of nutrition. In this connexion mention has already been made of the beneficial effects of school meals and school milk.

Equally important is the decline in the chronic infections, with their many manifestations in the skin. In 1909 deaths from tuberculous in Britain numbered about 58,000 In 1950 the deaths were about 15,000 although the population at risk was much increased. In the past few years the control of tuberculosis in cattle has made such rapid strides that veterinarians are already beginning, half seriously to express their fears that tuberculosis-free herds may be re-infected from human sources. The outlook for the control of tuberculosis is now bright. Mass radiography the early supervision of contacts, and vaccination with BCG together with the improvements in therapy should make this disease of relatively minor importance within a few years. Certainly the statistics are encouraging. From 1851 to 1910 the mortality from tuberculosis declined steadily at the rate of one per cent per annum. During the past three years progress has become really fast, for 1949 showed a 10 per cent decline over 1948 and 1950 a 20 per cent decline over 1949 MacKenna (1952) has pointed out that tuberculous disease of the skin was formerly commonly found among the inhabitants of city slums, because these persons lived in ill-ventilated, overcrowded rooms and were frequently undernourished. Lack of education very often results in the disease being concealed until it has reached an advanced stage In addition to lupus vulgaris and scrofuloderma the group of tuberculides contributed to the pattern of skin disease. If it be accepted that approximately 40 per cent of tuberculous infections of the skin are caused by the human and 60 per cent by the bovine type of bacillus, then some indication of the future incidence of these diseases may be gained from the fact that of deaths in children in England and Wales between 0 and 5 years in 1950 only 615 were due to tuberculosis of all forms—125 respiratory and 490 non-respiratory Whereas during the decade 1921–1930 little milk was effectively pasteurized (none until after 1924 and less than 15 per cent in 1930) by 1938 about 98 per cent of the milk consumed in London was effectively pasteurized as compared with less than 50 per cent in the rest of England. For 1950 the respective percentages were 99 5 and 80. Ninety-nine per cent of the milk in the schools is now pasteurized or derived from tuberculin-tested herds, and

THE PRESENT DAY

The State emerged from World War II with a complete range of welfare services, of which the National Health Service forms part. This Service is sharply divided into administrative compartments into hospital and specialist, general practitioner, and local health authority services, but the practice of dermatology remains, [illegible] a matter for the clinician working in hospital and in the home. Many of the men now in practice acquired their knowledge from teachers familiar with the form [illegible] of thirty or forty years ago, and it may not be unprofitable to review the present position, and try and deduce from it the possible shape of things to come.

Changes in age distribution

Take the first changes in the people themselves. The population of these islands now numbers about 49 millions, with a density of about 600 to the square mile. Whereas fifty years ago the expectation of life was less than 50 years, it is now [illegible] years from birth for men, and 70 or more years for women. If they succeed in reaching those years they may expect to go on to [illegible] or 80 years of age. The change in age distribution was well shown by Miss Hornsby Smith (1952) in her address to the Institute of Almoners. She said:

> Now there is a particular item which today presents a very grave problem with which often many of you find yourselves confronted, and that is the care of old people. I do not need me to tell you the difficulty of that problem in relation to the numbers of old people for whom, at one time or another, we have to make provision. I would remind you that 100 years ago there were nearly [illegible] persons of the working population to every [illegible] over sixty-five. At the present time there are only [illegible] persons of the working population to [illegible] old age pensioner, and by [illegible] it is estimated that the figure will be down to 4. Put in another way, there were [illegible] million persons over sixty-five in 1900 and there are expected to be [illegible] million by [illegible].

Some of the results of this change in age-structure, which affect all Western nations in greater or lesser degree, are well brought out in a recent study by [illegible] and his associates (1952) in the United States. They found that whereas since 1900 the death rates in [illegible] important diseases had declined, it had increased in the following [illegible] groups: diseases of the heart, cancer and other malignant tumours, diabetes mellitus, congenital malformations, ulcer of stomach or duodenum, diseases of [illegible], [illegible] and [illegible]. They commented that "a country with an ageing population must look forward to a constant increasing aggregate number of persons disabled by illness for two months or more, unless it can achieve success in combating chronic illness and the degenerative diseases." It is not unreasonable to suggest, therefore, that [illegible] must be reflected in dermatology [illegible] and that the skin afflictions of the older age-group will come increasingly under the notice of the practitioner. Side by side with the increase in age of the population has gone a decline in the birth rate, [illegible] between 1870 and [illegible]. In those few years the average size of family has declined from five or more children to slightly over two. Small families require only small houses, and where both parents must go out to work, [illegible] including [illegible] rather than medical.

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Equally important is the decline in the chronic infections, with their many manifestations in the skin. In 1909 deaths from tuberculosis in Britain numbered about 58,000 In 1950 the deaths were about 15,000 although the population at risk was much increased. In the past few years the control of tuberculosis in cattle has made such rapid strides that veterinarians are already beginning, half seriously to express their fears that tuberculosis-free herds may be re-infected from human sources. The outlook for the control of tuberculosis is now bright. Mass radiography the early supervision of contacts, and vaccination with BCG together with the improvements in therapy should make this disease of relatively minor importance within a few years. Certainly the statistics are encouraging. From 1851 to 1910 the mortality from tuberculosis declined steadily at the rate of one per cent per annum. During the past three years progress has become really fast, for 1949 showed a 10 per cent decline over 1948, and 1950 a 20 per cent decline over 1949 MacKenna (1952) has pointed out that tuberculous disease of the skin was formerly commonly found among the inhabitants of city slums, because these persons lived in ill-ventilated, overcrowded rooms and were frequently undernourished. Lack of education very often results in the disease being concealed until it has reached an advanced stage" In addition to lupus vulgaris and scrofuloderma the group of tuberculides contributed to the pattern of skin disease. If it be accepted that approximately 40 per cent of tuberculous infections of the skin are caused by the human and 60 per cent by the bovine type of bacillus, then some indication of the future incidence of these diseases may be gained from the fact that of deaths in children in England and Wales between 0 and 5 years in 1950 only 615 were due to tuberculosis of all forms—125 respiratory and 490 non-respiratory Whereas during the decade 1921–1930 little milk was effectively pasteurized (none until after 1924 and less than 15 per cent in 1930) by 1938 about 98 per cent of the milk consumed in London was effectively pasteurized as compared with less than 50 per cent in the rest of England. For 1950 the respective percentages were 99 5 and 80 Ninety-nine per cent of the milk in the schools is now pasteurized or derived from tuberculin-tested herds, and

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Take the first changes in the people themselves. The population of these islands now numbers about 49 millions, with a density of about 600 to the square mile. Whereas fifty years ago the expectation of life was less than 50 years it is now 65 70 years from birth for men and 70 or more years for women If they succeed in reaching those years they may expect to go on to 77 or 80 years of age. This change in age distribution was well shown by Miss Hornsby Smith (195?) in her address to the Institute of Almoners. She said

> "Now there is a particular item which today presents a very grave problem with which often, many of you find yourselves confronted and that is the care of old people You do not need me to tell you the difficulty of that problem in relation to the numbers of old people for whom in one way or another we have to make provision I would remind you that 100 years ago there were nearly 13 people of the working population to every 1 over sixty-five At the present time there are only 6 people of the working population to 1 old age pensioner and by 1977 it is estimated that the figure will be down to 4 If I may put it another way there were a million people over sixty five in 1861 and there are expected to be 8 million by 1977 "

Some of the results of this change in age structure, which affects all Western nations in greater or lesser degree are well brought out by a recent study by Bachman and his associates (1952) in the United States. They found that whereas since 1900 the death rates in 21 important diseases had declined it had increased in the following 8 groups diseases of the heart, cancer and other malignant tumours, diabetes mellitus, congenital malformations, ulcer of stomach or duodenum, diseases of prostate, biliary calculi and exophthalmic goitre They commented that A country with an ageing population must look forward to a constantly increasing aggregate number of persons disabled by illness for twelve months or more unless it can achieve success in combating chronic illness and the degenerative diseases It is not unreasonable to suggest therefore, that this trend must be reflected in dermatology also and that the skin afflictions of the later age-groups will come increasingly under the notice of the practitioner Side by side with this increase in age of the population has gone a decline in the birth rate, which fell by 60 per cent between 1870 and 1939 In those few years the average size of family has declined from five or more children to slightly less than two Small families require only small houses and where both parents must go out to work disabling diseases, including affections of the skin become matters of major concern requiring perhaps institutional care on grounds which are social rather than medical

special treatment units for modern therapy Unfortunately the short-stay patient does not, even today form the major problem. At the end of 1949 about 40,000 beds in mental hospitals and institutions were occupied by patients aged 65 years and over and of those in mental hospitals 21 per cent had a diagnosis of senile dementia. With the increasing age of the population the proportion of senile mental disease may be expected to increase, and to impose thereby a heavier burden on the already overloaded mental services. The interplay of mind and body is reflected more clearly and quickly in the skin than in any other organ of the body and early and efficient psychological investigation would pay a high dividend in the reduction of many disabling skin lesions, but it is obvious that if the major efforts of the psychiatric services are absorbed by the care of the psychotic and the senile, early and efficient care of others must suffer in some degree. The answer seems to lie in an extension of preventive psychiatry Even that disheartening disease schizophrenia, of which more than ten thousand cases were admitted to mental hospitals in England and Wales in 1949 may quite possibly be prevented, or its effects minimized, by preventive action in childhood. "Treat the mother" is an accepted axiom in certain diseases of the skin in infancy and it might well be extended, in the form of a joint effort by the hospital consultant, the general practitioner and the local health authority so that the susceptible child may be quickly seen and his home environment investigated. The principle of prevention could also readily be applied to many of the psychological problems of the adult and the elderly

Conditions in Industry

The changed outlook of society and of the individual, during the past fifty years are well shown in industry Long and irregular hours of work, in dirty and ill-ventilated work-rooms, have been replaced by well-regulated conditions. The employment of children is no longer tolerated, and the health of women is now safeguarded. The adolescent undergoes medical examination before employment, and dangerous trades are carefully supervised, while those who prove to be unsuitable for employment in one form of industry may be resettled in another These measures, together with improved cleanliness and better protection by clothing, barrier creams and the control of toxic processes, and readily available medical and nursing advice, have made many factories safer than the home. Indeed, it may be said that the housewife is now more at risk than her sisters in industry for she works without protection or supervision, and increasingly uses compounds to which her degree of sensitivity is unknown. Both she and the rural worker tend to live on the job whereas the factory worker has a regular break, during which he may rest, wash and eat at a properly appointed canteen. Although much remains to be done, and particularly in improving conditions in the small factories where most of the work of the country is done, there is no doubt that working conditions are incomparably better than those of former years, and the individual is no longer prepared to "put up with" abnormalities of the skin without seeking advice. Women, in particular are quick to notice and report blemishes. On the other hand industrial processes are now complex, and the opportunities for contact with potentially dangerous compounds, the toxic effects of which may be only partially known, are more numerous. Here also the rural worker may be at a disadvantage, for he is now handling fertilizers, and weed and

the remaining percentage includes a proportion of dried milk. With control of the human carrier and of tuberculous milk both of which are within sight, the tuberculous affections of the skin should assume a role of minor importance in western countries, comparable perhaps with that of leprosy today

The venereal diseases show a somewhat similar picture. By 1950 the number of new cases of syphilis attending venereal diseases clinics in England and Wales had dropped to about 4 000 and those of first year congenital syphilis to 227 The incidence of gonorrhoea was also much reduced The results of modern treatment are already appearing in the decline in deaths from late manifestations, such as general paralysis of the insane and tabes dorsalis With the control of syphilis a cause of disease of the skin about which many volumes have been written will disappear The Report of the Ministry of Health for 1950 (Part II) confirms that the home reservoirs in infectious syphilis at present stand at a record low level but that it is as well to realise that they would rapidly become flooded in a national emergency and that they continue to be fed by a constant importation of infection from overseas The fact remains that a disease which has towered over all others for centuries with the exception of tuberculosis, is now reduced to attacking about one in eleven thousand of the population of Great Britain, and with vigilance at the Ports, energetic contact tracing and extension of routine blood tests" may be relegated to a comparatively minor role.

Malignant disease

In 1950 more than 85 000 people in England and Wales died from cancer as compared with 70 000 in 1940 Of these, malignant neoplasm of the skin claimed only 554 men and 474 women representing a proportion of 13 male and 11 female deaths per 1 000 total cancer deaths. The principal cause in the increase of cancer mortality has been the rapid rise in cancer of the lung in men, for cancer mortality in women has declined slightly since 1938 but it is interesting to note that the mortality from leukaemia (including aleukaemia) rose by 58 per cent between 1938 and 1950 The current discussions on the advisability of publicity campaigns for the early diagnosis of cancer have relatively little application to malignant disease of the skin for the notification of its presence is there for all to see. It is surprising, however to note how long a lesion can be left before expert advice is sought.

Mental disease

Perhaps the most alarming statistics are those relating to mental disease. About half the total number of beds in Great Britain are devoted to the care of mental patients and the mentally defective, and they are inadequate for the purpose, both in number and in quality By the American standard of five acceptable mental beds per thousand population many more beds would be required than are in use at present, but, apart from this, most mental hospitals are ill-equipped for the work they now have to do for they are no longer merely places in which to segregate the hopelessly insane for their own safety and for the protection of society The proportion of voluntary patients has increased rapidly since 1930 and, if the nature of the buildings would permit, mental hospital practice would now approximate closely to that of the large general hospital with an extensive out patient service, short stay in-patient accommodation designed for a rapid turnover of patients, and

special treatment units for modern therapy Unfortunately the short stay patient does not, even today form the major problem. At the end of 1949 about 40,000 beds in mental hospitals and institutions were occupied by patients aged 65 years and over and of those in mental hospitals 21 per cent had a diagnosis of senile dementia. With the increasing age of the population the proportion of senile mental disease may be expected to increase, and to impose thereby a heavier burden on the already overloaded mental services. The interplay of mind and body is reflected more clearly and quickly in the skin than in any other organ of the body and early and efficient psychological investigation would pay a high dividend in the reduction of many disabling skin lesions, but it is obvious that if the major efforts of the psychiatric services are absorbed by the care of the psychotic and the senile, early and efficient care of others must suffer in some degree. The answer seems to lie in an extension of preventive psychiatry Even that disheartening disease schizophrenia, of which more than ten thousand cases were admitted to mental hospitals in England and Wales in 1949 may quite possibly be prevented, or its effects minimized, by preventive action in childhood. "Treat the mother" is an accepted axiom in certain diseases of the skin in infancy and it might well be extended, in the form of a joint effort by the hospital consultant, the general practitioner and the local health authority so that the susceptible child may be quickly seen and his home environment investigated. The principle of prevention could also readily be applied to many of the psychological problems of the adult and the elderly

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insect destroyers, of great potency He has, however one great advantage over his counterpart in industry he works at his own pace. Also although he may travel considerable distances to work and be subject to exposure to the elements (most countrymen succeed, however in keeping their shirts dry") he is spared the fatigue of the rush hour The cumulative effect of daily travel each night and morning, perhaps with several changes from train to bus or tube, must be considerable. The rural worker also is spared the frustrations and disappointments, and the nervous tension of success or fear of failure, which beset the urban dweller It is doubtful whether any natural disaster or set back can be half as serious in its effects on the individual as, for example, the passing over of an urban worker who expected and anticipated promotion Equally serious may be the penalty of success in one who is temperamentally unfitted for responsibility In a nutshell then it may be said that while industrial hygiene, and the environment of the worker have improved the compounds with which he works have, like his daily life, become highly complex.

FUTURE TRENDS

It is against this rapidly changing background that the future pattern of dermatology must be determined and here the non-expert is at a disadvantage, by reason of the intricacy of the subject. To attempt to relate some 300 skin diseases to current environmental and social change would tax a modern Solomon, but fortunately it is possible to break the subject down, at least to some extent. Perusal of the seventh edition of the *Nomenclature of Disease* compiled under the *aegis* of the Royal College of Physicians of London together with the tables of contents of current text books, shows that it is possible to detach from the main structure acute and chronic infections, the parasitic diseases, conditions due primarily to physical and chemical causes, and diseases due to vitamin deficiency Other trends may be deduced indirectly as, for example, those associated with increased nervous stress, or with increasing age.

Infective and parasitic conditions

Take first the conditions of the skin associated with cocci and parasites. It is generally agreed that autogenous self-disinfection of the skin must break down before these conditions can become established. In other words the skin must become unhealthy a process which it shares with the body as a whole, and which
... of person, clothes and surround-
... d be possible to trace changes
... The Report of the Chief
Medical Officer of the Ministry of Education (1952) shows that there has been a remarkable decrease in the number of children known to have received treatment for certain skin diseases during the past five years. Cases of impetigo, for example, numbered more than 64 000 in 1947 but only 27 000 in 1951 Perhaps a better indication of the improved condition of children may be given by the number
... In 1908 when the first report of the Board of
... one half of the number of girls in urban
... ie figure was about one quarter In 1951
the figure was 6 per cent of the entire school population. While this is admittedly disappointingly high there is general agreement that the incidence of lousiness in

schoolchildren is decreasing, and that severe degrees of infestation are now rarely seen. The problem seems to have reached the "hard core" stage when the new insecticides, however powerful they may be, can make no impression against the ignorance and fecklessness of a small section of the population. A similar picture is given by ringworm, which in the early years of the school medical service constituted one of its greatest problems. In 1951 only 2,365 schoolchildren in England and Wales had ringworm of the scalp. As the incidence of scabies has also declined (from about 38,000 cases in schoolchildren in 1947 to 4 723 in 1951) the general trend seems clear Regular inspection, skilled treatment, adequate nutrition, and education of the public designed to reduce the numbers of the socially irresponsible, should suffice to reduce the common infective and parasitic skin disorders to a low level from which they can only be raised again by some great disaster such as another war With their decline should go many other conditions, such as boils and carbuncles, ecthyma, staphylo-streptodermia, and eruptions due to sensitization of the skin as a result of pyogenic infection.

Dermatitis due to physical and chemical causes

A field of investigation which is likely to require increasing attention in the future is that of dermatitis due to physical and chemical causes. The potential victims may include people such as housewives and domestic and rural workers, but, while the range of potentially irritant substances is increasing almost daily so that any attempt at classification soon becomes out-dated, the types of reaction are limited, and the requirements for prevention are gradually becoming clear Chief among these are the selection of suitable personnel, and the provision of good working conditions. Heat and perspiration tend to increase the risk, particularly in those with fair dry skins, and the importance of cleanliness of surroundings, clothes and person is now well-recognized. So also is the use of barrier creams, but above all there remains the level of education and intelligence of the workers, so that they may recognize the risks, and take full advantage of the protective facilities made available to them. Here it is perhaps advisable to stress the need to educate also the medical student, for the general practitioner especially in rural areas cannot be expected to recognize conditions about which he has not been warned, and which he sees but rarely

The changes in the pattern of disease, as discussed so far might be said to apply almost universally for the differences are rather those of time and locality than of fundamental change. The counterpart of the European mediaeval city may still be found in other parts of the world, and so also may the adverse working conditions, particularly for women and children, which existed in Britain for many years after the Industrial Revolution. Sepsis, parasitic infections, and malnutrition still loom large over much of the world as causes of disease, including that of the skin. How large may be deduced from a consideration of the child population of the world. Dr Martha Elliott (1949) has estimated that of the 700 million children in the world some 60 million are in North America, 27 million in South America, 185 million in Europe (including 60 million in Russia) and 360 million in Asia and Oceania. With 55 million births each year it is obvious that improvements in environment, and in maternal and child care, are likely to aggravate rather than alleviate suffering, unless measures are also taken to increase food supplies and raise social standards.

So far also we have considered mainly the effects of environment, for better or worse, on mankind. The physical surroundings, the viruses and pathogenic bacteria and parasites do not, unfortunately represent the whole story The most important member of man s environment is his fellow-man, and he has the unhappy knack of creating emotional and psychological difficulties for himself which are of more far reaching importance than, say sensitization reactions induced by bacteria He is also reaping the harvest of his efforts to improve his surroundings, for he is now in western countries at least, living to an age when he becomes liable to many conditions which appeared only rarely when death came early Consider for a moment this inter relationship of man with man. Britain before the industrial changes was primarily based on a rural economy with a small population whose members had a short expectation of life. In the space of less than 300 years the population of these islands has expanded tenfold, so that each man must keep his elbows into his sides to give his neighbour room. John Donne s prophecy that No man is an island entire of itself every man is a piece of the continent, a part of the main any man s death diminishes me, because I am involved in mankind" has now come true. No longer are we content merely to share the common air with all living creatures through it we send messages instantaneously to all parts of the world, and through it we seek to pass at ever increasing speed. Little more than 100 years ago a war was fought and won in India before the news of its outbreak reached this country Today the sensitive patient may have his eczema aggravated by anxiety as to what a statesman several thousands of miles away may say the day after tomorrow Anyone who doubts the growth of communal life has only to study the uniformity of education transport and food in western countries or better still, the sharing of blood by blood transfusion (in 1950 nearly half a million bottles of blood, each containing about three-quarters of a pint and each the gift of one donor were issued by the National Blood Transfusion Service in England and Wales) Almost every action of the individual is subordinated to the requirements of society and the primitive emotions and instincts, by which our bodies are still governed, must be controlled no matter what the price. That the price is heavy every physician, and certainly every dermatologist, is well aware, for the results show readily in those organs most closely associated with the mind namely the cardiovascular system, the digestive tract, and the skin In England and Wales in 1950 approximately 250,000 deaths out of the total of 510 000 occurred from disease of the cardiovascular system, while disorders of the digestive tract accounted for 11 2 per cent of the total illnesses and injuries investigated by the Social Survey in that year (Annual Report of the Ministry of Health, 1950) In the final report of the Dermatology Committee of the Royal College of Physicians (1947) the comment is made that the incidence of skin disease in general practice is about 6 per cent of all cases, and that in industry the loss of man-hours due to occupational dermatitis exceeds that in every other form of industrial disease. This figure is supported by the findings of the Social Survey (1950) which gives the percentage of medical consultations for diseases of the skin as six, while the proportion of total illnesses and injury due to this cause was 3 per cent. Equally important is the fact that diseases of the skin accounted for 3·6 per cent of the total days of incapacity

Bettley (1949) found in his own practice of dermatology that over 80 per cent of cases fall into ten or a dozen common diagnoses, while hundreds of uncommon

and rare diseases make up the remainder and the same author gave more detailed statistics at a recent meeting of the Section of General Practice of the Royal Society of Medicine. He showed that the incidence of different dermatoses among 18,273 new patients seen at St. John's Hospital for Diseases of the Skin, London, in 1951 included 36 per cent belonging to the "eczema-dermatitis" group, with seborrhoeic dermatitis coming next, and the thirteen most frequent diseases making up no less than 78 per cent of the total (Bettley 1952).

All writers are agreed as to the importance of psychological upset on the development of eczema, and the part that emotional or psychiatric factors play in skin disorders in general, including those found in industry. While the term psychosomatic disease is now somewhat less in favour than it was it has its uses, for it emphasizes, in a way that no other term does, that the main requirement of the disorders so listed is peace of mind. How that is to be obtained is, indeed, a problem for society for it implies the reconciliation of the emotional and spiritual requirements of the individual, at home and at work, with the vast and impersonal machine of which he forms part.

PROBLEMS OF AN AGEING POPULATION

Finally there come, at ever increasing speed, the problems associated with an ageing population. Foremost among these are the tumours. Fortunately epithelioma of the skin, both basal-cell and squamous, declares itself early and control of these malignant growths is a relatively simple matter for the expert, but the cumulative cost to the community is considerable.

Less alarming, but the cause of much discomfort and misery for the aged, are the simple growths of the epidermis. Corns and callosities have not the same sinister connotation as, for example, leucoplakia or senile keratosis, but they and deformities of the feet and toe nails, may prove to be the last straw in rendering an infirm person immobile. It is not too far fetched to suggest that the services of a chiropodist may quite literally keep an old person out of hospital. There is no need to enumerate the affections of the skin in the elderly or the circulatory disturbances, including gangrene which come with increasing age, but it may be profitable to discuss for a moment their prevention, for unless they can be prevented, their cost to the community quite apart from the suffering of the individual, is going to increase greatly in the near future. Already more than 10 per cent of the population has reached the age of 65 years or over and in twenty-five years time the proportion will be considerably higher than this. There is no simple solution for the prevention of onset of ailments which come with increasing age, but one fact stands out clearly they start from small beginnings. If it were possible to encourage routine medical examinations from early middle life many conditions would be detected which are now neglected until drastic remedial action is required. By means of antenatal care, the infant welfare and school medical services, and the examination of the adolescent before employment and in the armed forces, the health of the young is now reasonably well safeguarded. By an extension of this process it should be possible to prevent, or at least postpone, many of the afflictions of middle and later life.

ENVOI

Human ecology has been defined as the relationship of man to his environment. Nowhere are the stresses and strains of the efforts to adapt to our surroundings more clearly shown than in the skin, and dermatologists should therefore be able to assess clearly the success or failure of the many recent developments in human welfare. It could be said, without undue exaggeration, that man has succeeded so well in controlling his physical environment that he must now begin to solve problems which only a few years ago did not exist. With increasing numbers, and increasing complexity of life, he has to face mental and emotional stresses for which the traditional wisdom now rapidly being forgotten, provides no precedents, and with in many instances, nothing to replace the ancient spiritual values. The under nourished and disease ridden member of some primitive community might well elect, if he had the power to retain his physical discomforts rather than face the mental unrest of a highly civilized industrial community where every disaster is foreseen often magnified many times, in advance of its coming. Certainly it is a nice point whether it is better to live a full and contented but relatively brief life, than to survive to experience the long process of degeneration and decay however well cushioned by society Fortunately the dermatologist can in a changing world, still follow Martial's advice *Memento in pellicula cerdo tenere tuo"*

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CHAPTER 2

A CRITICAL EVALUATION OF PSYCHOSOMATIC MEDICINE IN RELATION TO DERMATOLOGY

IDA MACALPINE

INTRODUCTION

THE LITERATURE on psychosomatic aspects of skin disease is not difficult to catalogue except perhaps for what has been called the "avalanche of contributions" and the growing number of incidental references in dermatological, medical psychological psychiatric, psychoanalytic and other journals and books But to report individual results and findings without comment is to add to the confusion already existing, particularly as much of the literature is of a tentative and speculative nature although frequently presented as factual

It appeared to the writer therefore, more useful and consistent with the purpose of this volume to analyse the peculiar and inherent difficulties and intricacies of the subject, and undertake the task of giving a critical overall view in particular to take stock of the obscurities which seem to have arisen and continue to exist, *owing to the different lines of approach to the problems.*

Research into psychosomatic aspects of cutaneous disease is a domain which is shared by general medicine and dermatology by psychiatry and psychoanalysis, *by general physiology and neurophysiology All these disciplines differ in their* approach to the problems each uses its own methods, techniques and vocabularies each derives its impetus from either theoretical or therapeutic interest and thus they differ widely in respect of their immediate aims. Nor are these various disciplines closely knit homogeneous entities they are themselves subject to considerable cleavage they overlap and all are influenced by the vagaries of fashion. Many are today so highly specialized that it is usually difficult, sometimes impossible to judge whether a contribution from a different speciality is sound or fallacious speculative or proved original or humdrum

To throw into relief these difficulties, differences and divergences, in so far as they touch on psychosomatic research will be our first task thus equipped questions of method and treatment will be briefly discussed and lastly an outline given of such trends and findings as appear to the writer important, fruitful or promising.

To subject the problem itself to precise scrutiny may be of greater service to progress than to stress apparent agreement. Inherent in this attempt *is the* danger that the reviewer's own attitude and predilections may—in fact are bound to—appear unduly in the foreground. But no helpful survey can be written except it be critical and no criticism can be offered except through the medium of the writer's own views and experience. The impression of personal bias will, however be mitigated if the vantage point from which such assessments are made is clearly *stated* It is of course impossible in short compass to do justice to so broad a subject as psychosomatic medicine in relation to dermatology to appraise its

position fully would entail reviewing its own history as well as that of medicine, dermatology and psychiatry. Further the social background of the day would have to be considered, shaping as it does contemporary thought in all things, even science.

GENERAL OBSERVATIONS

It is not strictly accurate to speak of psychosomatic aspects of skin disease, or even of psycho-dermatology as an entity. Granted there exists a group of psychosomatic illness in medicine, it is both non-clinical and artificial to limit this concept to one isolated organ or system. Disease entities or syndromes, other than the purely dermatological, in which the skin is also involved, whether as yet clearly delineated or not, would thus be easily overlooked. Further the terms suggest a tripartite division, namely mind, body and skin.

It has been said that the reason why it has been difficult to introduce psychological concepts into dermatology was "because dermatologists know too little about psychological medicine, and medical psychologists too little about dermatology" (Wittkower 1948). The more profound reason and the greater obstacle seems to be that both disciplines are not sufficiently aware and appreciative either of their own and still less of each other's difficulties, lacunae, uncertainties, incompatible tenets, fashions and foibles. In short it is the present state of dermatology and the baffling position in psychiatry which are the student's greatest handicaps. As the writer's main concern is with psychiatry an outline of the present-day situation in that speciality will be given first.

The psychiatrist

The gulf that exists between psychiatrist and dermatologist is small compared with that between psychiatrists of differing outlook and practice. First there is the big division into those psychiatrists who work with psychotics in mental hospitals and those who work outside often exclusively with psychoneurotic patients. These sub-specialities are further divided into a section of *psychiatrists* who attempt to express mental illness in terms of somatic processes or search for somatic processes to explain mental illness and those who believe that the mind must be studied and understood in its own terms. The last-mentioned group is again sharply divided into those who believe in unconscious processes and those who do not. One could go further and enumerate other schools, for example the group of social psychologists who interpret human behaviour exclusively in terms of social adaptation or maladaptation and those who believe that human behaviour can be understood through the study of animal behaviour and conditioned reflexes.

To make matters still more complicated and obscure, these divisions are far from clear cut. For instance one of the most confusing features of the present-day situation is a development which aims at a direct *link-up* between unconscious mental processes and their neuro-physiological or biochemical (somatic) basis and manifestations. It seems almost as if the fact that the dermatologist deals with the visible and measurable and the psychiatrist with the invisible and immeasurable were the least difference between the two and the smallest difficulty to overcome. Research into psychosomatic disorders is so intricate and elusive because it deals first and foremost with the mind: this is a difficulty which concerns the dermatologist as well, but primarily the psychiatrist.

The dermatologist

These complexities of psychiatry are not always clearly realized In psychosomatic research, for instance, there is not infrequently found a notion that clinical psychology is and should be *nothing more than the application of* "*common sense*" to clinical problems Because psychological terms lend themselves to free, easy and inexact usage, they are often bandied about with *superficial familiarity without* appreciation or sensibility" (Wood Jones 1946) The underrating of one discipline by another is not calculated to improve the status of either or to encourage serious workers to enter the no-man's-land of psychosomatic research. Much that has been written on psychosomatic medicine may rightly be condemned as nebulous, irrelevant or unscientific but it must be remembered that a psychiatric study *may* be *valid* and valuable without appearing to be "common sense" in the *same way as studies in the more exact* and measurable branches of medicine.

This dangerous lack of appreciation of the status of each other's discipline is well illustrated by the paradoxical situation which has arisen While dermatologists publish long studies on psychiatry (Cormia 1951) or even dispute with each other over purely psychiatric issues such as the value *of projection tests* (Cormia, 1951 Obermayer 1952) psychiatrists and psychoanalysts tend more and more to invade cerebral anatomy neuro-physiology and biochemistry and to express opinions on the need or indication for medical and surgical treatment.

The impetus

Historically seen it is perhaps true to say that the greatest impetus in the search *for psychic factors in* cutaneous *disease* has come from *therapeutic needs*, that is, from the fact that many dermatological conditions are refractory to routine physical treatment Added to this many conditions with which the dermatologist deals are of a chronic or recurrent nature, as well as of unknown aetiology The emotional strain to which the dermatologist is continually exposed appears to the intruder into this discipline greater than that in many other branches of medicine greater perhaps even than in psychiatry because in that field patients usually do not clamour so persistently for *help* *This therapeutic frustration* is driven home with each patient who produces a visible lesion or persisting symptom which cannot *be ignored or minimized*.

It is interesting to observe that in surgery and gynaecology psychosomatic possibilities are less vigorously pursued although the incidence of psychosomatic conditions can with safety be assumed to be proportionately at least as high But the surgeon can either interfere actively or he can refer the patient elsewhere whereas the dermatologist has to admit to and continually face fairly sharply defined therapeutic limitation

The aim

If interest in possible psychic origins of cutaneous disease derives its main impetus from therapeutic needs research must necessarily be influenced by this. It is in fact divided into a search primarily directed at helping as many patients as possible to get better and secondly into research into psychic events and the mechanisms by which these can explain skin lesions These two aims are very different neglect *of this distinction* leads to confusion as when quick therapeutic results or their lack are used to substantiate or exclude psychic factors, and results

of superficial psychiatric examinations used as contributions to the theory of psychosomatic illness or again when a psychiatric study is judged of little value because therapy is not thereby improved.

Co-operation

The student of psychosomatic conditions should be trained in all branches of mental disease, psychoneuroses, psychoses and allied disorders. Ideally he should be so well equipped as to be able to withstand the currents of medical fashion, and avoid being hidebound by his psychiatric or psychoanalytic training. Otherwise investigations will be prejudged in the light of his allegiances, instead of theory being built up on the results of clinical investigations. For example it will be shown that research into psychosomatic conditions has been influenced largely by the body of psychoanalytic knowledge which was built up from study of the psychoneuroses, hence emphasis has tended to be on a presupposed similarity between psychoneurotic and psychosomatic symptoms. This view is strengthened by the common notion that to be psychotic is equivalent to being "insane" and therefore institutionalized. Psychosomatic patients by the very fact that they are about are wrongly considered as of necessity psychoneurotic (Wertham, 1949). It was recently shown (Gaw Reichard and Tillman, 1953) that latent and ambulatory—prepsychotic—forms of schizophrenia are "much more common than is generally thought" Overt alienation is a manifestation of advanced psychosis, and the absence of frank delusions and hallucinations, for long the hall mark of the mad" by no means excludes the diagnosis or justifies the faulty though common diagnosis of psychoneurosis (Bleuler 1911).

If the psychiatrist brings an all-round knowledge and experience to bear on dermatological problems he is still at a great disadvantage compared with the dermatologist. He only sees such patients occasionally and then they are usually highly selected cases already subjected to much physical investigation and treatment. He is therefore deprived of the steady stream of clinical impressions of dermatological patients of all types, and lacks the dermatologist's direct observation as well as the opportunity of comparing organic with psychosomatically determined conditions. This may account for the many publications which give the impression of existing *in vacuo* of being concerned with abstract considerations and theoretical speculations rather than with living patients. This is also one reason why psychosomatic studies seem more concerned with problems of classification than with the elucidation of pertinent clinical observations and individual facts.

The case material

Closer contact between dermatologists and psychiatrists or perhaps even between psychiatrists and skin patients would allow of a wider selection of patients, and avoid patients being selected for psychiatric investigations after prolonged unsuccessful trials with physical treatment. How fruitful such close co-operation can be was shown by the work of Barber and Gillespie. It may be considered provocative to suggest that a psychiatrist might even attempt to select psychosomatic patients by other than dermatological classification or other customary criteria but the psychiatrist is in a position to pick out earlier signs of psychiatric disorder than the dermatologist and would thus be able to point out a possible connexion between mental state and a skin lesion of unknown origin.

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presence of emotional difficulties or conflicts of whatever severity or type is of course in itself no proof of any direct, least of all causal relationship with a skin symptom. This point raises questions as to methods in psychosomatic research, of which more will be said later. Historically viewed such a situation is not unique and probably is an unavoidable phase in the early history of any new subject. Eventually advances may depend on the application of new techniques of investigation developed from many varied approaches to a problem (Stokes and Beerman, 1948).

FORMULATIONS OF THE PROBLEM

The term "psychosomatic" is used by some to embrace all relationships between body and mind in a general manner. "All medicine, by definition, must be psychosomatic" (Seguin, 1950) by others only when the mind is believed to play the greater part in producing symptoms. Others again apply the term "somatopsychic" to conditions in which the mind is influenced by bodily processes. But as has been pointed out (MacKenna and Macalpine, 1951), if the term "psychosomatic" is to cover all inter-relationships between body and mind in an indeterminate manner no new term need have been coined to emphasize the time-honoured knowledge that there are such inter-relationships. If the concept of "psychosomatic" is to serve any useful purpose and achieve precise status it must first of all be narrowed down to a fairly exact definition. When for instance tuberculosis is held to be a psychosomatic disease because emotional factors may play a part, it is clear that the time has come for the term to be severely limited if it is ever to achieve a particular meaning as an aetiological concept. It even happens that the term is used in different senses in one article and its connotation in a particular context has often to be divined. Understanding between workers is frequently stultified by the fact that they are not really discussing the same issue.

Philosophical aspects

If one tries to unravel basic trends in psychosomatic discussion and research today one is surprised to find that much of the controversy is of a philosophical and semantic rather than of a medical and scientific nature. There are the various issues, explicitly raised or implied whether it is legitimate to speak of cause and effect in psychosomatic illness, whether it is appropriate to think in terms of one cause or a multiplicity of causes (Straus, 1953) further whether it is permissible to equate causality and aetiology whether one ought to think in dualistic fashion of mind as opposed to matter or whether mind equals matter and if not now perhaps at some future date. Finally the often crucial issue as to whether a contribution to the subject is valid within the meaning of the reader as opposed to the meaning of the author.

Not a little confusion and worry for instance seems to be caused by the question of "why" the skin is chosen in a given case for the symptom. But then the question "why" is not a legitimate one to ask of the natural sciences both question and answer lie in the realm of philosophy. Natural science answers the question "how". It is interesting that this question is often as of necessity posed at the end of a psychiatric study and is fortuitously answered by reference to constitutional and hereditary factors or by introducing terms such as "somatic

The practice of patients being sent to the psychiatrist as a last resort has great disadvantages for all concerned. First, for the patient who is exasperated and often feels that he is sent because the dermatologist is at his wit's end secondly for the dermatologist, because he in turn will be exasperated by the psychiatrist if the latter cannot achieve a cure and lastly for the psychiatrist, because he will be goaded into trying to achieve therapeutic results at all costs, or else give an opinion or assessment of the patient on too little evidence, the process of classification serving to release him from therapeutic effort Such pressure is not conducive to painstaking and unbiased investigation it leads to procedures in psychiatric therapy to be discussed later which may harm the patient and which make it impossible to gain insight into psychopathological processes which might account for the skin symptom The recently revived interest in physical treatments, hypnotism and similar methods bears witness to this fact as does the fashion of assessing personalities instead of making a psychiatric diagnosis.

One wonders whether the early tendency in psychosomatic research towards classification (establishing personality types and profiles, conflict patterns and focal or nuclear areas of conflict") all supposedly specific for particular affections did not derive some of its driving force from attempts to explain psychotherapeutic failures or even stem the growing demand for psychotherapy

Therapeutic results are of course not to be despised even if they do not provide insight into mental processes But they should not be used as the basis for theoretical discussions and conclusions as to why a skin patient developed his lesion nor even is the conclusion always justified that a condition improved by such methods was of psychosomatic origin

Such quick results as are achieved sometimes unintentionally and surprisingly even by diagnostic interviews, set a problem in themselves well worthy of study they are by no means confined to psychotherapeutic endeavour even minor medical procedures such as the exhibition of drugs may achieve such an effect

SCOPE OF THE TERM "PSYCHOSOMATIC"

The great variety of approaches to psychosomatic medicine is not always realized Of course as long as there is no generally accepted definition many supposedly psychosomatic conditions are bound to be investigated from all angles with such an origin in view

Unfortunately the term "psychosomatic" is sometimes applied to illnesses which cannot be accounted for in other ways in the present state of medical knowledge. Under such conditions the term is only serving a stop-gap function This criticism applies in some measure to the use of the term in dermatology but equally to other branches of medicine. On the other hand doubtless many conditions now considered organic (some allergic" phenomena for instance) may be shown one day to belong in reality to the psychosomatic group Cases of idiopathic light sensitivity provide a case in point (Barber 1952a Macalpine 1953b)

Again, some workers start off with the assumption that emotional factors are responsible for a given condition patients are then investigated to this end, and when such emotional factors or conflicts are found the conclusion is drawn that the original premise was correct and aetiological conclusions and definitions follow accordingly A circular argument is thus introduced and continued The

term neurodermatitis altogether and to speak only of skin disease of known origin on the one hand and of psychogenic skin disorder on the other relegating to an idiopathic, i.e. undiscovered realm those in which neither of these descriptions apply"

The psyche

It is important to realize that the basis of this controversy is not only semantic. Behind it lies hidden the antithesis of mental (psychic or psychogenic) and "neuro" (nerves or somatic). Hence the fundamental difference between speaking of a psychological disorder as opposed to the somatic physical processes or pathways by which lesions are produced. This diversity of approach not always clearly appreciated or stated, makes evaluation of contributions so difficult. Some papers taken as claiming psychic origin for a malady are really studies in physiology

Parallel treatment as criterion

Many writers circumvent the tricky questions of aetiology and causation by suggesting that those disorders be designated as psychosomatic in which both physical and psychological treatments should run concomitantly From a theoretical point of view little advance can be expected from such wide undefinable terms of reference. From a practical point of view much can be said in principle against the efficacy of treatments which keep the patient also in doubt as to the nature of his illness This point will be taken up later when discussing questions of treatment.

PSYCHOANALYSIS

Psychoanalysis must be considered under a special heading because all psychopathology is in the last resort based on it But psychoanalysis has been built up on and for the psychoneuroses and has little to contribute directly to somatic symptoms, either in theory or practice, other than the hysterical. Studies using the classical psychoanalytic technique are therefore few and far between and somatic symptoms are treated *ipso facto* as of the same order as say phobias or obsessions, that is to say they are automatically equated with purely psychic symptoms.

The study of psychosomatic medicine has, however been taken up by certain psychoanalysts, particularly the Chicago group, and startling developments are at present taking place. Not only is the soma stressed, but all psychic events are the subjective reflection of physiological processes (Alexander 1952). "A psychosomatic diagnosis is defined as "essentially a medical diagnosis which includes the complete psychiatric evaluation of the personality factors" (Alexander 1957). The term psychosomatic should be used only to indicate a *method of approach* both in research and therapy namely the simultaneous and coordinated use of somatic—that is physiological, anatomical, pharmacological, surgical and dietary—methods and concepts *on the one hand*, and psychological methods and concepts on the other The question may be raised whether the psychosomatic approach should be considered as a transitory method which will be abandoned as soon as we are able by improved electroencephaly and other physiological techniques to study those brain processes which to-day yield only to psychological methods (Alexander 1952).

compliance" and libidinization of the skin" But, faced with a case of say lupus vulgaris, dermatologists are satisfied to show that the tubercle bacillus is responsible for the lesion that they do not proceed to ask why it is affecting the skin in preference to other organs in the body does not invalidate their findings.

Semantic aspects

Hecht (1952) writes It cannot be emphasized often enough that there is no such entity as a psychic disorder of the skin. It is merely a question of how much psychic factors and how much somatic factors contribute to the aetiology precipitation or prolongation of the dermatosis Disagreement with this statement will be seen to be of a semantic nature and revolves around psychic disorder of the skin In these terms would acaraphobia be or not be a psychic disorder of the skin? The expression itself is of course a verbal absurdity It is as little a psychic disorder of the skin as it is a dermatological disorder of the mind

It must not be thought that such controversies are new Gull (1868) wrote "The causes of hypochondriasis is an expression even more singularly unhappy than the average instances of a phraseology of causation applied to those circumstances which precede the outward and visible development of functional disorders He recommends instead of speaking of causes simply to speak of conditions under which symptoms arise. If these fundamental terms and formulations were clarified much unnecessary misunderstanding would be avoided.

Functional versus organic

Confusion is added by the old issue of functional versus organic. Again semantics seem to play the biggest part The term "functional" can be found used with different connotations by different workers and also in different disciplines Does organic or structural change in the skin make a skin symptom organic to the exclusion of being functional? Is functional to be equated with psychic? Is there a transition from one to the other as there is a transition from health to disease, or are they mutually exclusive?

"Neuro" versus mental (psychic)

Becker and Obermayer (1947) in a paragraph on psychiatry speak of "nervous exhaustion and neurocirculatory instability" as the cause in a number of dermatoses which they list as psychosomatic. They suggest that the study of functional elements in association with organic diseases and of functional disease itself be centralized under the designation of neurosomatic medicine rather than psychosomatic medicine "

Sulzberger and Baer (1951) on the other hand find these outworn and confusing terms Earlier Gillespie (1938) had also felt that "some of the existing dermatological terminologies in relation to psychogenesis seem a handicap which could easily be cleared away In particular the affix neuro might well be dispensed with, or be confined to those cases in which a physical and not a psychological origin is denoted i e when a truly functional—as far as anyone knows—nervous disorder is at the bottom of the condition, and when the functional was not dependent on a psychological disorder I find it very hard to conceive what a functional disorder of the nerve can be It would be best to discard the

term neurodermatitis altogether and to speak only of skin disease of known origin on the one hand and of psychogenic skin disorder on the other relegating to an idiopathic, i.e. undiscovered realm those in which neither of these descriptions apply

The psyche

It is important to realize that the basis of this controversy is not only semantic. Behind it lies hidden the antithesis of mental (psychic or psychogenic) and "neuro" (nerves or somatic) Hence the fundamental difference between speaking of a psychological disorder as opposed to the somatic physical processes or pathways by which lesions are produced. This diversity of approach not always clearly appreciated or stated, makes evaluation of contributions so difficult. Some papers taken as claiming psychic origin for a malady are really studies in physiology

Parallel treatment as criterion

Many writers circumvent the tricky questions of aetiology and causation by suggesting that those disorders be designated as psychosomatic in which both physical and psychological treatments should run concomitantly From a theoretical point of view little advance can be expected from such wide undefinable terms of reference. From a practical point of view much can be said in principle against the efficacy of treatments which keep the patient also in doubt as to the nature of his illness. This point will be taken up later when discussing questions of treatment.

Psychoanalysis

Psychoanalysis must be considered under a special heading because all psychopathology is in the last resort based on it. But psychoanalysis has been built up on and for the psychoneuroses and has little to contribute directly to somatic symptoms, either in theory or practice, other than the hysterical. Studies using the classical psychoanalytic technique are therefore few and far between and somatic symptoms are treated *ipso facto* as of the same order as say phobias or obsessions, that is to say they are automatically equated with purely psychic symptoms.

The study of psychosomatic medicine has, however been taken up by certain psychoanalysts, particularly the Chicago group and startling developments are at present taking place. Not only is the soma stressed, but all psychic events are the subjective reflection of physiological processes" (Alexander 1952) "A psychosomatic diagnosis" is defined as essentially a medical diagnosis which includes the complete psychiatric evaluation of the personality factors" (Alexander 1952). The term psychosomatic should be used only to indicate a *method of approach* both in research and therapy namely the simultaneous and coordinated use of somatic—that is, physiological, anatomical, pharmacological, surgical and dietary—methods and concepts on the one hand, and psychological methods and concepts on the other The question may be raised whether the psychosomatic approach should be considered as a transitory method which will be abandoned as soon as we are able by improved electroencephaly and other physiological techniques to study those brain processes which to-day yield only to psychological methods (Alexander 1952)

Psychoanalytic physiology

This is a complete *volte face* and its connexion with psychoanalysis is almost only in name the word unconscious hallmark of psychoanalysis, does not appear in the index of *Psychosomatic Medicine* (Alexander 1952). Study and investigation of purely psychological events is no longer the centre of interest. All attempts are directed at trying to superimpose psychodynamics on neurodynamics, or conversely deduce psychodynamics directly from neurodynamics without the intervention of the psyche. Whether neurophysiology stands to gain from the introduction of psychological terms like regressive behaviour" or to what extent knowledge of the mind of man will be improved by being translated into physiological terms, remains to be seen In the meantime psychoanalytic neurophysiology is on the map and "analytic investigators are now turning their attention to basic physiologic and pathological phenomena as well as to motor-sensory behaviour patterns during the analytic session In this way it may be possible to obtain more reliable psychosomatic correlations *in statu nascendi* (Deutsch 1952)

It is clear that with this movement the difference between analytically and non-analytically orientated psychiatry will disappear as well as clinical distinction between types of mental disease, that is the diagnosis as also the difference between somatic and psychic processes "The dichotomy between body and mind if we understand psychic phenomena as the subjective aspect of certain physiological (brain) processes disappears (Alexander 1952)

Sherrington (1951) from the side of the neurophysiologist uttered a stern warning against such premature attempts The mental is not examinable as a form of energy That in brief is the gap which parts psychiatry and physiology" A similar view is taken by Walshe (1953)

Division of opinion among dermatologists

It is evident that the very problem as to what constitutes psychosomatic illness, is not as yet defined in a generally acceptable form It is therefore not surprising to find that dermatologists differ widely and fundamentally as to which illnesses should be considered psychosomatic. Comparison of the long list of Becker and Obermayer (1947) of psychosomatic dermatoses with that of Sulzberger and Baer (1951) shows how wide the gulf can be.

Siemens and Jagtman (1951) even devoted a study to excluding psychological factors altogether The automatic regularity with which admission and spontaneous cure on the one hand and relapse and return home on the other coincide in any age group establishes for the first time experimental proof of the fact that *psychic factors* have no appreciable influence on neuro -dermatitis

CURRENT APPROACHES

Methods

Perhaps most misunderstanding in psychosomatic research is caused by the variety of methods employed according to the side from which the subject is approached Methods must differ according to whether the somatic concomitants of an emotion are being studied whether on the assumption that mind

equals matter mental processes are being investigated as physical manifestations or whether the mind is being studied in its psychic relations. In the present state of knowledge results from one field cannot, however great the temptation, be translated into the other Results must be judged in, and their application confined to, the terms and methods of the particular investigation.

Whereas in natural science the particular is explained by the general according to law the study of psychic relations relies on the historical method according to which a given event is explained by a preceding one. In psychosomatic research, therefore, a single well conducted case study will be more revealing than evidence based on numbers of not so closely studied cases the objection often raised, that this method is in principle unscientific and of the "I had a case" variety is not valid. Barber (1952b) and Lomholt (1952) put in timely pleas for the lucid and extensive study of individual cases.

Statistical Evidence

Under pressure from the physical side of medicine, "proof" of results of psychological investigations is often asked for in terms of the natural sciences. This has led psychiatrists away from the more disturbing, exacting, time consuming and seemingly less rewarding study of mental processes into attempts at statistical investigations based on superficially assessed, subjectively chosen, arbitrarily assembled traits of personality

But statistical inquiry is not the royal road to understanding, let alone demonstrating so complex a subject as psychic events. Sherrington (1951) stated that

thoughts, feelings, and so on are not amenable to the energy (matter) concept. Therefore they lie outside Natural Science Mind is not open to quantitative measure

Attempts at introducing methods into psychosomatic research the results of which would lend themselves to statistical treatment, led to short-cut assessments of personality as an array of static separable entities. Some workers have even felt that psychological tests of the projective variety in particular the Rorschach, would supply the necessary information without the intervention of the psychiatrist But tests have only a place as possible aids to the clinical psychiatrist in special circumstances by themselves they can never replace the clinical approach and the insight gained during psychotherapy Investigations based exclusively or predominantly on such tests are dangerous over-simplifications and as misleading and unrevealing as any scientific short cut.

Controls

Such studies are not improved by the controls so frequently demanded. These cannot be expected to serve their purpose because psychosomatic symptoms are not fixed entities, but are more dependent on dynamic quantitative than on static qualitative factors. Whether or not symptom formation occurs may depend on a ery small alteration within the psyche. This is precisely what makes psychotherapy possible, and accounts for the wide spontaneous variations in the severity of psychosomatic conditions, even total remissions. Controls may therefore be expected to show the same psychic constellations, which neither invalidate nor confirm evidence of psychosomatic origin.

The raw material

Demand for statistical evidence has naturally led to the endeavour to use large numbers of patients in any given investigation The reader is then confronted by an imposing array of figures which detract attention from their meagre foundation Frequently such findings expressed in statistical terms are based on single interviews with patients nevertheless far reaching conclusions are drawn. For instance Hall-Smith and Norton (1952) report results of a psychiatric survey of a random sample" of 150 dermatological patients based on interviews which lasted half to one hour On several occasions the patient was actually walking to the door at the end of the interview before he let slip significant information One might be excused for wondering what further information would have been forthcoming in subsequent interviews.

Thus the raw material on which statistical studies are based is inadequate, fragmentary and unconvincing more often than is commonly realized It is the writer s experience and considered opinion that "assessments" of personalities are to be regarded with suspicion and that they can never replace the careful pains taking clinical investigation observation, and stocktaking which can only take place during psychotherapy and which indeed is psychotherapy

Selection of patients

It is sometimes stated that selection of patients for investigation should be avoided because otherwise results and findings may be biased. However it should be remembered that there is no valid objection to selection *per se* On the contrary the possibility of new findings and insights may depend on the proper deliberate, perhaps ingenious selection of patients for investigation

Results of psychotherapy

There is clamour from all sides that results of psychotherapy should be made available in statistical form Although it is obvious that much might be gained by compiling such figures, this is feasible only if at all in the most general terms. Patients for instance may show alleviation of depression or anxiety without improvement in their psychosomatic symptoms On the other hand in some cases symptoms improve or disappear rapidly but the patient is either no better mentally or may even be considerably worse. How is one to express such important facts in figures? And again what value have figures which do not pay regard to such facts?

The same difficulties apply to the length of time the patient ought to be free from symptoms in order to be listed as improved or cured. This question in particular is fraught with difficulty in psychosomatic skin conditions which mostly run a remittent course with a natural tendency to spontaneous improvement

These points are made here because pressure of unjustified demands by dermatologists on psychiatrists, as also by psychiatrists on psychiatrists for evidence of their results tends to lead to hasty pseudo-scientific publications.

Evaluation of therapeutic results

This is in medicine in general a formidable and risky scientific task and one to be approached with the greatest caution in every branch In dermatology in particular it is unwise to draw definite aetiological conclusions from results of

either physical or psychological treatment, whether they be positive or negative. It is extremely doubtful whether the satisfactory outcome resulting from a given treatment can reveal the cause of an eruption first because psychological factors enter into every physical treatment to some extent, whether recognized as such or not and in the same way as physical illness may be refractory to physical treatment, so may symptoms originating in the psychic sphere be resistant to psychotherapy Further "many a psychogenic disorder can be cured pharmacologically and many an organic disorder can be influenced favourably by psychotherapy (Dunbar 1949).

These cautions are mentioned in order to warn against too ready evaluation of therapeutic results, in particular against using them as evidence for theoretical discussions and conclusions. When taken in conjunction with other supporting evidence they have of course a definite place

Personality Types

Stokes (1930) introduced the idea of "tension frame of mind" as being responsible for skin diseases of psychosomatic origin this was meant to be a signpost, not a definitive statement. Great impetus to research was given by his initiative. MacKenna (1944), in attempting to correlate certain skin diseases with certain personality make-ups stated a fact which is undeniable that in a general manner certain groups of people tend to have certain diseases. Both were giving frames of reference only

Both concepts, however have since received specific interpretations hardly intended. Further they have been used as if they were aetiological explanations rather than merely tentative descriptions of the setting in which certain diseases occur Tension, stress, even distress, and personality are all used today as if they were circumscribed definable entities.

The study of personality profiles and types has been largely developed by Dunbar and her approach has been taken up on a large scale in fact correlations between psychosomatic diseases and personality types have formed the majority of contributions. Such studies, although they have their origin in the psychoanalytic school, are phenomenological and descriptive, not aetiological and dynamic, for which they are often mistaken because of the use and misuse of psychoanalytic terms.

At the present time, as its limitations are being realized, early enthusiasm is slowly giving way to a more critical attitude and the recent tendency has been away from this approach. It is objected for instance that such correlation between specific personality and disease, one personality one disease, is proving erroneous (Frank, 1951) and that no diagnostic or therapeutic advance is thereby made.

Different psychosomatic affections may appear in the same person simultaneously but the more usual phenomenon is that of alternation or sequence, of different affections (Halliday 1943).

Further it has been pointed out that the difference between the various personality profiles diminishes as they are applied to more and more diseases "The differences are indeed very finely drawn, and at times so finely drawn as to defy separation (Miller and Orton, 1952). The same criticisms apply to such concepts as areas of focal conflicts and "specific emotional situations" In

illustration an undue craving for infantile dependence on the mother has been claimed to be the focal conflict specific successively for patients with asthma, peptic ulcer eczema and tuberculosis, and has now been enlarged to serve as universal pathogen for all psychosomatic disease "Every case of psychosomatic disorder has its origin in the mother-child relation of dependency" (Sperling, 1952)

Some authors, Grace and Graham (1952) for instance, have shifted the factor of specificity to particular life situations in conjunction with particular completely conscious attitudes to them" Urticaria occurred "when a patient saw himself mistreated" and asthma in situations from which the patient wanted to be away

On the other hand Cobb (1950) an early supporter of investigating type of personality as an aetiological factor in psychosomatic disease, now writes the question is whether the personality profiles used in psychosomatic research are worth anything at all From the dermatological side Graciansky and Stern (1950) Obermayer (1952) and Davies (1951) for example, could find no correlation between specific personalities and specific skin lesions MacKenna and Macalpine (1951) criticized this approach on both theoretical and clinical grounds.

Specificity

Psychological investigations which attempt to correlate specific conflicts, personality types or life situations with specific dermatological entities, naturally have to adhere to strict dermatological classification They presuppose first that dermatological classification as it stands today is absolute and final and secondly that "focal conflicts and specific emotions have only one specific form of somatic expression.

Neither of these tacit assumptions is proven indeed certain facts rarely given due consideration throw serious doubt on these premises. It is only necessary to mention that various dermatological and other conditions may occur in a given patient either at the same or at different times.

That dermatological classification is not final is suggested by Shaffer and Beerman's (1951) attempt to find a common basis on clinical and histopathological grounds for lichen simplex chronicus, prurigo nodularis, lichenificatio gigantea, and certain phases of the Sulzberger-Garbe syndrome" It was found that "these different expressions of emotionally induced lichenification can be accounted for on the basis of an acceptable psychodynamic mechanism Schur (1950) meanwhile, on the basis of a psychoanalytic study of a patient with the Sulzberger Garbe syndrome, claimed that for the first time a big incurable dermatological entity of unknown origin could be explained as the dermatological manifestation of a neurosis Three more cases of the same entity were studied they showed essentially the same structure" The question "What determined the choice of the organ in these cases?" is left unanswered but "once the skin is chosen it becomes an extremely handy organ for expressing the conflicts around narcissism, exhibitionism, aggression, masturbation, compulsive trends, etc."

This is an example of studies not of psychosomatic conditions, but of psychoneurotic patients with incidental skin lesions. The latter are treated as of the same order as psychoneurotic symptoms, "as the dermatological manifestations

of a neurosis" (Schur 1950). Such studies have inadequate dermatological and psychiatric foundations, and exemplify the neglect of psychiatric diagnosis.

Instead of investigating a single diagnostic entity Macalpine (1953b) selected patients with facial dermatoses, diagnosed as light sensitivity contact dermatitis, permanent erythema with burning and itching, urticaria, angio-neurotic oedema of lips and eyes, Besnier's prurigo some patients presented with menopausal lesions of the eyelids as described by Barber (1934). It was found that anger was the underlying unconscious emotion. In all patients there was a direct relation to depression, because depression is a complex affect in which anger anxiety and guilt are fused. A true depression is avoided while the anger finds outlet in the facial lesion, which can therefore be assessed as a "masked depression" This explained the high incidence of middle-aged women. Paranoid attitudes and over sensitiveness to the complaints were considered pathognomonic of psychosomatic as distinct from organic facial lesions.

In summary investigations into psychosomatic origins have taken as their starting point mind, character personality conflict, body adaptation stress, distress, environment, immaturity of the ego conscious and unconscious processes, as well as various physiological approaches. One point emerges clearly from all this namely the lack of mental theory in psychiatry The various approaches to psychosomatic research throw this lack into sharp relief

THEORY OF MENTAL DISEASE

The fundamental problem is really this that there is no unanimity whether mental illness—psychosomatic illness included—originates within the mind for unknown reasons or whether as the result of interpersonal conflicts, whether caused by faulty adjustment, or finally whether the environment itself can be the *sole factor* in producing mental illness

The commonest current conception of mental illness is the one which visualizes it in terms of maladjustment. Hence all mental illness is unwarrantedly equated with the psychoneurotic, that is with fairly mature mental mechanisms. The supposition that it is always the outcome of a lack of or faulty adaptation is for the observer the easiest and least disturbing way of regarding mental ill health. It keeps at bay appreciation of unconscious factors fraught with all the dangers of the unknown and uncanny from which the observer may not be exempt. Maladaptation as the cause of mental illness also introduces a modicum of moral uplift for the observer that is the psychiatrist It allows him to think of himself as well adjusted and to assume the role of preceptor towards the patient, who is told to pull himself together and shoulder his responsibilities Perhaps for these reasons the factor of infantile dependence in the patient has so quickly and easily achieved the status of universal pathogen in this field.

Many examples of this attitude could be given. Sulzberger and Zaidens (1948) for instance, discussing the role of emotional factors in the production of somatic disease, say that in a neurotic personality where everyday life situations cannot be solved with relative equanimity illness is frequently used as a cloak for personal inadequacies

This is an over-simplification it is a moot point whether all mental symptoms can be explained on this "mature" basis of lack of adult adaptation. *Lack of adaptation* may with the same justification be taken as the result and not as the cause of the illness Whatever the nature and origin of for instance psychotic symptoms they are more primitive, *simpler in mechanism and may originate* entirely within the person's mind

For all these reasons there is not even agreement whether to speak of psychosomatic illness, states, personalities, reactions conditions, or simply of psychosomatic symptoms

The immediate task, *therefore, seemed to be to approach the subject from a* different angle namely to delineate the psychosomatic symptom and its formation in its psychiatric and clinical aspects in particular to differentiate it from psychoneurotic (hysterical) symptoms with which it is commonly confused. Better understanding of how symptoms arise might lead to diagnosis from psychiatric *aspects as well as visible or invisible* manifestations, and thus give psychosomatic symptoms clinical status in their own right Having their own diagnostic criteria the lengthy detour of diagnosis by exclusion of organic causes would also be avoided

PSYCHOSOMATIC SYMPTOM FORMATION

Where psychosomatic conditions have been studied by psychoanalysis, they have in their dynamics been treated as if they were *a priori* the same as those found to apply to psychoneurotic symptoms. The obvious difference between the two namely the somatic part of the symptom, has been disregarded except by Alexander and his school who attempt to consider both on a purely somatic basis.

The psychoneurotic (hysterical) symptom expresses a conflict or idea, often in symbolic form It is a compromise formation between unacceptable sexual impulses and repressing forces It is based on comparatively mature mental mechanisms In compensation a fairly large measure of secondary (social) gain is extracted from the environment.

In a study of psychosomatic symptom formation (Macalpine, 1952) the following differences were stressed

(1) Psychosomatic symptoms run a remittent and sporadic course, whereas the psychoneurotic tend to persist

(2) In the therapeutic situation transference behaviour is different

(3) The psychosomatic symptom can and must be traced to a recent reality stimulus, psychoneurotic symptoms being caused by instinctual conflict

(4) The psychosomatic symptom is not a defence against instinctual drives opposed by the super-ego and unacceptable *to the personality*

(5) Secondary or social gain is inconspicuous or absent

Other points noted were

(6) What the patient himself believes to be the cause of his illness turns out as a rule to be a "cover cause" that is, its significance lies in its unconscious meaning Precipitating events *must not be taken at their face value*, and cannot be evaluated without appreciation of their unconscious significance. Reference to particular times of day dates anniversaries or even seasons may like an unconscious memory be traced to significant reality factors or events. In this connexion it is of interest

that conscious major upsets in patients lives are rarely followed directly by the outbreak of psychosomatic disturbances.

(7) Not only is the patient unaware of the significance of the reality stimulus but he is also unaware of the emotions or fantasies thereby activated.

(8) The psychosomatic symptom may be defined as rudimentary disguised, somatically expressed emotion or fantasy The patient is unaware of the emotion or fantasy expressed in his symptoms. The emotion only achieves partial expression, so that instead of leading to action and thus subsiding, it persists. It is this persistence which produces pathological changes, that is, the symptom.

(9) The psychosomatic symptom is therefore not a defence mechanism of the mature mind but is more primitive and characterized by a partial breakthrough and persistence of an unconscious emotion or fantasy It is not caused by a need for symbolic dramatization of conflict, but is a direct expression of the primitive body-mind unit.

(10) In all its features the psychosomatic symptom resembles more closely the psychotic than the psychoneurotic Instead of leading to action and change of the outside world, changes are confined to the body whether in altered sensations or functions It is autoplastic instead of alloplastic, and therefore divorced from reality

(11) It is not intended to imply that patients with psychosomatic symptoms are psychotic the description refers to the psychopathological mechanism of symptom formation. Such symptoms may occur in psychotic, psychoneurotic or "normal" people. It might therefore be more precise to speak of psychosomatic symptoms rather than of psychosomatic states and illness.

PSYCHOSIS

Several recent studies have followed the same trend of a possible relationship between psychotic and psychosomatic symptoms. For instance, Appel and Rosen (1950) report several patients in whom psychosomatic and frank psychotic illness alternated, and they suggest that a reciprocal relationship exists between them. They also on the basis of this finding utter a note of *warning against* too ready disregard of the function of psychosomatic symptoms, and the dangers of treatment whether by psychotherapy or by cortisone and ACTH" Similar relations have been noted by Funkenstein (1950). Swartz and Semrad (1951) noted the rarity of psychosomatic and McAllister and Hecker (1949) the rarity of allergic disorders in mental hospital populations. The frequency with which psychosomatic disorders alternate with psychosis was noted by Daniels (1951), and Rosen (1953) says that as patients improve from frank schizophrenic psychoses they develop hypochondriasis very often asthma " Joseph, Peck and Kaufman (1949) *report a case in which relief of* a dermatosis by means of psychotherapy was accompanied by the outbreak of a psychosis, a state of affairs also observed by the author who has seen psychosomatic conditions of all kinds alternate spontaneously and usually inversely with the severity of the psychosis, their development during spontaneous remission and their disappearance as a psychosis developed. Zaidens (1951) suggested that "psychosomatic disease frequently serves a purpose for the individual, in so far as it may spare that person a severe neurosis or psychosis"

Somatic Delusions

Somatic delusions are common in psychosis From the dermatological point of view *Wilson and Miller (1946)* reported delusions of parasitosis in frank psychosis. But *Wilson (1952)* extending his previous paper showed that delusions of parasitosis *also* occur in patients who show no other sign of mental abnormality He also noted that associated might be a variety of symptoms referable to bodily organs other than the skin

This brings out the important clinical fact that delusions in their mild form can be so isolated and every day that they escape recognition A gradual transition to psychotic hypochondriacal delusions from altered sensations and body functions, which in mild form may make their first appearance as psychosomatic symptoms, was suggested by Macalpine and Hunter (1953) Cornbleet and Brown (1948) mention that schizophrenics quite commonly seek "advice about some cutaneous sign or symptom long before the need for psychiatric attention is obvious"

Zaidens (1950) pointed out that hypochondriasis centred on the skin may express itself in delusions of parasitosis in milder degree patients may complain persistently and inordinately of dermatological lesions which appear minimal to the observer Gull (1868) pointed out the frequency in hypochondriacs of "heightened sensibility of the skin formication and burning pains"

Hypochondria

Such symptoms are classified as hypochondria which, although a stepchild in psychiatry and commonly confused with and mistaken for anxiety neurosis or hysteria belongs to the psychoses as concomitant or precursor or in all degrees of severity in its own right. Gillespie *(1929)* gave it the following description which incidentally he exemplified on a patient with skin lesions Overt anxiety is no part of a purely hypochondriacal state of mind one of the essentials is the absence of anxiety or similar affects hypochondriacal preoccupation is a type of interest a conviction and concern and not a fear of disease" He also noted that anxiety states and hysterias are often mistaken for hypochondria"

Summarizing relatively little is clearly understood about hypochondria or indeed about the prepsychotic stages of psychosis in which psychosomatic symptoms play the major role The patient's morbid or fantastic" concern with body function and sensation is neither explicable as the outcome of maladaptation to environment, nor as the mature—psychoneurotic—end product of mental conflict. Research on these lines promises to be fruitful.

TREATMENT

Nothing perhaps demonstrates better the diversity of approach and conception as to what psychosomatic symptoms are, than a glance at current therapies.

Abreactive techniques

The first aim of therapy is to relieve suffering, to help the patient get rid of disabling or embarrassing symptoms This is understood by some as a process similar to the removal of a foreign body and has led to methods of all kinds aimed

at achieving rapid results among these are hypnotic and the many abreactive techniques employing inhaled or injected drugs. Their rationale is to give the patient a chance to "let go in a non-specific way

Then there are techniques such as hypnoanalysis and narcoanalysis whereby attempts are made to uncover such unconscious material, trauma or emotion, as the patient does not, will not, or cannot reveal during interviews, but which "he must be made to face It is surmised that "confession" or "admission" will lead to cure. Garmany (1953) in contrast to Shorvon (1953) has recently found abreaction not only useless but potentially dangerous

Psychotherapies

Other therapies are based on the supposition that symptoms are due to the patient's faulty attitudes to life and persons he need only be told by the therapist where his reactions to the environment have gone wrong and need readjustment. Lomholt (1952), discussing Cormia s (1951) patients, slyly remarks "It might, for example, be asked whether it is a sign of health or disease to be well adjusted in the community surrounding these patients" Sometimes the necessity for re education is emphasized. Therapies based on these ideas take for granted a degree of omniscience and optimism in the therapist which is hardly realistic Manipulation of home and social environment is often considered an adjunct to such therapeutic measures curiously enough it is even held to be one particular type of psychotherapy

Psychoanalysis

Others again, particularly the psychoanalytic schools, believe that the psychosomatic symptom is only one facet of a generally faulty personality development, and hence a manifestation of a psychoneurotic make-up. Somatic and mental symptoms such as obsessions or phobias are not differentiated. Hence psychotherapy is envisaged as having to take the patient back to his earliest days, to the beginnings of his faulty interpersonal adaptation having reached the "fixation point he will under the therapist's guidance, be able to make a *fresh start*. Hence one reads much about "immature or inadequate personalities" narcissism and weakness of the ego often implying a moralistic judgment. As many of these terms are purely theoretical concepts, although commonly treated as factual, they are really more speculative and uninformative than they appear

All goes to show how uncertain, unscientific and chaotic psychotherapy still is how little is clearly understood or capable of systematization. The many new names—deep, short, vector direct, supportive and group therapies, etcetera—bear witness to this

Further the critical observer cannot fail to realize that lack of response to psychotherapy by no means shows that a symptom is not psychic or psychogenic thera peutic results can therefore *prima facie* neither be taken as confirming nor excluding psychic origin or significance of somatic symptoms.

In short, when symptoms fail to respond to psychotherapy it would be truer to say that they do not respond to psychotherapists, that is, to psychotherapy as it is understood and practised today

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Summarizing relatively little is clearly understood about hypochondria or indeed about the prepsychotic stages of psychosis in which psychosomatic symptoms play the major role. The patient s morbid or "fantastic" concern with body function and sensation is neither explicable as the outcome of *maladaptation* to environment, nor as the mature—psychoneurotic—end product of mental conflict. Research on *these lines promises to be fruitful*

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these body fantasies are often mild and loosely-held delusions. The patient half knows that they are "silly ideas" and is afraid after reassurance of making a fool of himself by continuing to talk about them. For the therapist it is all important that he be a good, attentive listener and that he can hold judgment in suspense until he is reasonably satisfied as to the correctness of his findings, a conviction which the patient must eventually share. If this is accompanied by corresponding improvement a good case has been made out for psychosomatic origin.

Response to psychotherapy

It is worth adding, because the contrary view is prevalent, that such patients, be they "normal" or latent psychotics, respond to adequate therapy more easily and quickly than do psychoneurotics. But the type of psychotherapy must be different. These patients are made worse, even psychotic, by methods which release still more unconscious material forcibly, as do for instance abreactive techniques. The classical psychoanalytic technique as advocated for the psychoneuroses is not only unnecessary but contra-indicated, as it also may be harmful. This is to be expected in view of the different structure of psychoneurotic and psychosomatic symptoms (Macalpine, 1950 and 1952). Psychoneurotic symptoms are a defence and thus a complicated mental end-product of instinctual conflict, originating in the sexual sphere; the psychosomatic—like the psychotic—patient suffers from a partial breakthrough of unconscious fantasies and emotions, which psychotherapy must help him to understand, deal with and ultimately repress again. For him the therapeutic situation of the classical "couch-free association" technique must be replaced by the "well structured situation of the face to face psychiatric interview" (Knight, 1953).

Parallel treatments

It is commonly held that psychological and physical treatments should run concomitantly; in fact definitions of psychosomatic conditions have been based on this postulate. But it is the writer's experience that such a regimen should be studiously avoided. A patient who after a diagnostic interview is believed to be "psychosomatic" can never take to the psychological approach wholeheartedly while he continues being seen and treated by the dermatologist. Not only will his loyalties be split between the two disciplines; he will, with some justification, take this double approach as a sign that his medical attendants also are far from being convinced of the value of their respective methods. Indeed, it can often be observed that treating the physical side as though this were of little importance is the best way of making the patient pluck up the courage to undergo psychotherapy; it may in fact be the decisive factor. Medical treatment confirms the patient's irrational, often delusional belief that he is suffering from a physical and not a mental symptom. This explains why patients with pruritus ani for instance are often made worse by surgical interference; even psychotic breakdowns are known to have followed. A similar point is made by Davies (1951), who believes that "local treatment ... merely concentrates the patient's morbid attention on his malady ... and may be worse for him than no treatment at all".

In this connection it is worth remarking on the fact that doctors generally see far greater danger in missing a somatic than missing a mental condition, although

Leucotomy and shock treatments

The intangibility of the psyche and the vagueness of our psychotherapeutic efforts combined with contemporary over valuation of action and the physical has led to by-passing the psyche altogether and to attempts to alter mind by altering brain. Leucotomy for instance, is described as "particularly applicable to states of distress and tension" (Henderson and Gillespie, 1951) Sargant (1951) summarized a paper on Leucotomy in Psychosomatic Disorders as follows Chronic tension, which is held by some to be responsible for the origin or perpetuation of many so-called psychosomatic disorders, can often be relieved by leucotomy it has therefore been used in various disorders eczema, asthma hypertension rheumatism anorexia nervosa and functional vomiting and cardiac neuroses He argues that leucotomy may break up abnormal physiological conditioning and allow a fresh start to be made" Without discussing this permanently mutilating operation one must point out that, perhaps spurred on by the spectacular advances in the physical sciences and medical therapeutics, psychiatry is in the grip of a *furor sanandi* which has given rise to the gibe that in its present state it seems to have little to do with either the "psyche or "iatry"

As in psychosurgery" so in the various forms of shock treatment no insight is gained into disease processes or mechanisms The basis of these unspecific methods and their efficacy are considered by Bleuler (1951) to be the same as the crude methods of the Middle Ages carried over into our time in the guise of refined techniques by which patients are shaken or shocked out of their morbid state.

The dermatologist as psychotherapist

Returning to psychotherapy the question is often raised whether the dermatologist can or should do his own psychotherapy or whether this should be done only by a psychiatrist A sensible and kindly dermatologist can often do more for his patient than a doctrinaire psychiatrist and one must agree with Ingram (1948) that " in a considerable proportion of cases of skin disease effective treatment demands no more than the taking of the history and clinical examination except that it should be shared and understood by the patient

The psychiatrist

It may be asked what sort of treatment the writer feels most suitable. In brief outline the psychiatrist should study his patient s conscious and unconscious mind, and be able to differentiate between the mechanisms governing each he should be particularly on the alert to detect and bring out negative transferences, and give the patient freedom to discharge his feelings. All in all he must try to understand the patient better than the patient can understand himself

It is important to detect pathogenic fantasies about body and bodily functions and trace them out with the patient. The only method to achieve this is to let the patient describe in the minutest possible detail, again and again if necessary what his complaint, for example, pruritus, feels like, what he thinks it may be, may be due to or lead to

Reassurance is rarely effective either it minimizes the patient s suffering or conversely he assumes that if reassurance is needed his complaint must be serious. Further he will avoid speaking about such odd ideas as he is harbouring, because

these body fantasies are often mild and loosely-held delusions. The patient half knows that they are "silly ideas" and is afraid after reassurance of making a fool of himself by continuing to talk about them. For the therapist it is all important that he be a good, attentive listener and that he can hold judgment in suspense until he is reasonably satisfied as to the correctness of his findings, a conviction which the patient must eventually share. If this is accompanied by corresponding improvement a good case has been made out for psychosomatic origin.

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In this connexion it is worth remarking on the fact that doctors generally see far greater danger in missing a somatic than missing a mental condition, although

it is beyond dispute that great even irreparable harm may be done by both physical investigations and medical or surgical treatments in a patient whose symptoms are psychosomatic or psychogenic.

SUMMARY

In broad outline, the approach by character personality types, and conflict patterns, the overvaluation of physical treatments in psychiatry and the legitimate interest in the patho-physiological aspects of psychosomatic symptoms are all acting to produce a somatic *psychosomatic medicine in which psychic relations* and events are relegated to second place, stereotyped or disregarded. This development repeats "the fundamental error or need of man of building psychiatry without psychology (Zilboorg, 1941) Advances in psychosomatic medicine in the future will depend first and foremost on the psychiatric study of patients.

CONCLUSION

Psychosomatic medicine has little substantial to show for its voluminous literature. It entered into a classificatory period before there was much to classify As so often in the history of medicine this tendency has been accompanied by lack of clinical interest in individual cases. If research can find its way back to the clinic, the study of single patients their symptoms and the workings of their mind, psychosomatic medicine, by providing a link between different specialties may *conceivably lead to advances both in medicine and in psychiatry* because of its close relation to dermatology it may lend additional weight to Pusey's (1934) contention that dermatology is the "Gadfly of the Mind"

SPECIAL TOPICS

Itching and scratching

It is surprising as Lomholt (1952) has reminded us that no monograph has yet been written on this, the leading skin symptom all the more so as in all its various aspects it is common ground for the dermatologist and psychiatrist

Studies have concerned themselves mainly with the physiology of peripheral mechanisms (Graham Goodell and Wolff 1951) investigated by means of itch powder *of necessity such investigations do not throw light on itching* which in the absence of manifest lesions is of central origin

From the psychiatric point of view Calnan and O'Neill (1952) found in 30 patients that itching of the skin as a single symptom or in association with excoriation or lichenification can behave like a stress disorder the reasons for the choice of the skin as a vehicle for discharge of tension were as a rule obscure No psychiatric insight can be expected from studies which do not differentiate between irregularly *scattered excoriations* pruritus ani, pruritus vulvae, itching of the head and cheek and lichen planus simplex (Vidal) type" Tension and stress are non-specific descriptive terms hence they allow such different skin conditions to be brought under one head. Understanding would be better furthered if the various itch scratch rub-knead-pick habits were carefully studied in single cases, and the distinction between pruritus with or without clinical signs (*sine et cum materia*) sharply maintained Much valuable information can be obtained for instance

from the observation (Shaffer and Beerman, 1951) that the itch is apt to develop at certain characteristic times for each individual patient. The patient's detailed account of what he feels at such times was found to be helpful in understanding patients with pruritus ani (Macalpine 1953a). It was interesting to note that these patients described their sensations in similar terms which were different from the terms used by patients suffering from other itching complaints characteristically patients with pruritus ani spoke of "tearing away"

Seitz (1951) in a study of a mixture of the same type of cases as Calman and O'Neill, found the *furor eroticus*, so often mentioned by previous workers, confirmed in the "compulsive and erotogenic attacks of excoriation" Their masturbatory nature" was revealed by patients clandestine and shameful attitude towards their scratching. It was assumed that excoriation also served as self punishment, and hence concluded that the term masochism "explained" the symptoms. Such statements are theoretical speculations and expositions, although by sheer weight of repetition they have acquired the status and dignity of clinical facts. The term "masochism" in its strict sense means solely a type of sexual perversion no evidence of the existence of sexual aberration in patients with the manifold varieties of itching skin complaints has been furnished.

The undisputed fact that patients attacks of scratching are commonly pleasurable at one stage, that they mount until a climax is reached and are then followed by a state of exhaustion is not sufficient evidence to equate them with, or regard them as a surrogate of sexual orgasm. Klauder (1936) also pointed out that the sexual and lustful elements of pruritus have been unduly stressed. The pain produced by scratching is a means of stopping the itching, explained physiologically by the fact that itching stops when pain supervenes (Rothman, 1941).

Warts

The possibility of removing warts by suggestion is customarily drawn as a red herring across psychosomatic discussion. Even a "case of Congenital Ichthyosiform Erythroderma of Brocq responded to hypnosis (Mason 1952). Such a finding is often taken as proof of psychosomatic origin Sulzberger and Zaidens (1948) find it a challenging fact "here indeed is the ideal place for future objective studies on the relationship of psyche and emotions to somatic *diseases*" *This* conclusion *is* based on the false belief mentioned above that what can be influenced by the mind must also have originated there. Bloch (1927), the first to investigate the treatment of warts by suggestion systematically rightly stressed that their cure by suggestion did not imply their psychogenesis.

Other conditions

Within the limitations of space no detailed account of findings in individual diseases can be given. The following points are thought worthy of mention. Psoriasis and acne vulgaris, it is felt, cannot be regarded as psychosomatic in the strict sense of that word. Investigations have been concerned with the acute stages and exacerbations that these are influenced by emotional factors does not warrant the conditions being labelled psychosomatic. Such exacerbations through emotional factors occur in purely medical conditions as well, although it is possible that skin conditions are more easily influenced by emotional factors, because the skin plays such a big part in emotional expression.

Conditions such as trichotillomania and dermatitis artefacta are undisputed psychiatric conditions played out on the skin and its appendages. The same is true for so-called neurotic excoriations.* But nothing fundamentally new has been reported. Alopecia totalis and alopecia areata still seem doubtful conditions on which judgment should be deferred until more evidence is available. The same may be said of lichen planus in the present state of knowledge.

Urticaria and angioneurotic oedema are in many cases without doubt found to have a psychic origin. The same applies to some cases presenting as contact



FIG. 1.—Mrs. E. M. aged 58 years. Two years' history of facial lesion diagnosed as contact dermatitis; psychotherapy then commenced, and the symptoms were found to be due to "retained tears." Patient had had two daughters, one of whom had been killed in her presence *during an air raid; the other died a year later of meningitis.* When after 10 years she was urged by friends to give up mourning and weeping for them, she developed the facial lesion. In retrospect it was found that exacerbations had coincided regularly with anniversaries relating to her daughters.

dermatitis (Fig. 1) allergic conditions, light sensitivity (Fig. 2) hyperidrosis and pompholyx and certain pruriginous eczemas, pruritus vulvae and pruritus ani (Fig. 3)

Pruritus ani

In an investigation during psychotherapy of patients with pruritus ani (Macalpine 1953a), it was found that although they were presenting monosymptomatically the pruritus never occurred alone: it was only the leading symptom in a syndrome. It always occurred in conjunction with gastro-intestinal complaints, such as indigestion, odd pains in the abdomen, constipation, feelings of fullness, flatulence, *haemorrhoids, a feeling of incomplete emptying at stool and of* the anal

* From personal observations and a perusal of cases in the literature it is evident that all patients who *inflict severe damage on themselves* must be considered psychotic. Hysterics (that is neurotics) characteristically avoid pain.

canal being too narrow and fissuring. Associated disturbances were also present in relation to sexual function, commonly frigidity and vaginismus in females and premature ejaculation or impotence in males.

These various complaints and sensations were traced to a common origin in a cluster of unconscious fantasies concerned with the interior of the body

In many cases the beginning or exacerbation of the pruritus was traceable to the reactivation in adult life of infantile unconscious fantasies centring on procreation taking place in the abdomen or intestines. These fantasies are primitive and develop before the infant has any knowledge of sexual function At this stage



FIG. 2.—Mrs. J. W age 21 years. For eleven years had attended various skin clinics and was eventually diagnosed as light sensitisation dermatitis without evidence of abnormality of porphyrin metabolism. The case, in fact, was entirely emotional in origin and was due to state of suppressed rage in girl of low intelligence, brought up under very poor and disturbed conditions, is the youngest of family of four sisters.

both boys and girls think themselves capable of having babies in their "tummies" and this idea is often reinforced by the advent of a younger sibling or early impressions of childbirth. Although this sounds absurd to grown-ups, such fantasies acted out in the body can frequently be observed in children's play a healthy boy of two was found running around as if in pain and in explanation said that he was having kittens as the cat had had the day before Food fads can often be traced to such archaic unconscious fantasies.

As the child matures, the girl has to carry over her ideas of oral and anal impregnation and intestinal pregnancy to the woman's adult baby-producing capacity the boy has for ever to abandon the notion that he too can have babies in his body That this is not always successfully accomplished is shown by the widespread custom of the *Couvade*

Such fantasies are incompatible with adult life and mature thinking in either

sex. Reactivation is highly disturbing, more so in the male, because such "fantastic" ideas are not only contrary to nature and reality but also imply a change of or doubt in the nature of his sex. Hence the greater severity longer duration and

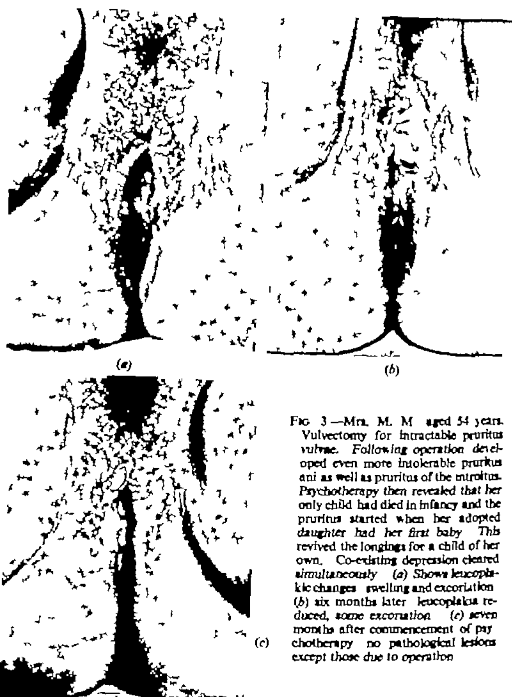


Fig 3—Mrs. M. M aged 54 years. Vulvectomy for intractable pruritus vulvae. *Following operation developed even more intolerable pruritus ani* as well as pruritus of the introitus. *Psychotherapy then revealed that her* only child had died in infancy and the pruritus started when her adopted *daughter had her first baby* This revived the longings for a child of her own. Co-existing depression cleared *simultaneously (a) Shows leucoplakic changes* swelling and excoriation (b) six months later leucoplakia reduced, *some excoriation* (c) seven months after commencement of psychotherapy no pathological lesions *except those due to operation*

greater general disturbance in male patients These findings also account for the hitherto unexplained two to one preponderance of male to female cases and throw light on these patients curious habits often commented on in the literature eager ness *to be examined with lack of modesty regular self inspection by means of*

mirrors, constant talking in detail of their self-styled "dirty" and "disgusting" complaint, their custom of referring to their "condition" rather than to their disease, and lastly their being puzzled and concerned rather than anxious.

Many of these habits have received the interpretation of veiled homosexuality. This, however, cannot be the explanation, because it fails to account for pruritus ani in women. Female homosexuals have no particular interest in the anal zone. These habits are, in fact, the outcome of doubt and uncertainty in the nature and function, or possible change of his sex. What he seeks is reassurance that his body fantasies are illusory.

In pruritus ani these fantasies do not reach conscious appreciation, but find expression in altered body feelings and paraesthesiae. By thus remaining preconscious psychotic delusions are avoided. In schizophrenics fantasies of abdominal or intestinal pregnancy break through into consciousness in the form of frank delusions and hallucinations.

Reality situations acting as precipitating factors in the revival of these archaic fantasies were traced in three-quarters of the male patients to pregnancy, childbirth or miscarriage in a near relative, and in women to frustration of childbearing either by miscarriage, death of a child, menopause or operation. Other frustrating situations can have a similar effect (Fig. 3).

The almost regular finding of cancerophobia usually centred on the bowel, or conviction of infection can be taken as symbolic expression of procreation fantasies—of something growing "inside".

Customary treatment by ointments and x-rays were rarely found effective and if so only temporarily. Surgical interference often proved harmful—in three patients leading to psychotic breakdown. Such measures are taken by the patient as confirmation of his irrational belief that something needs cutting out or away.

Psychiatrically pruritus ani is to be regarded as a hypochondriacal syndrome, accompanied by concern and preoccupation with body function. It can shade into schizophrenia, but often occurs in the absence of other psychiatric abnormality. It should be clearly differentiated from anxiety hysteria or neurosis.

The syndrome is capable of reduction by psychotherapy. Strangely enough duration and severity do not influence accessibility to psychotherapy adversely: patients with incapacitating symptoms for 15 years can be so much improved as to be almost symptom-free in 20–30 sessions. The presence of pronounced paranoid trends tends to worsen the prognosis, whereas depressive features are on the whole more favourable.

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CHAPTER 3

CUTANEOUS SENSIBILITY

G Weddell

INTRODUCTION

It is still generally assumed that there are four primary modalities of cutaneous sensibility and that the sensory pathways have components specific for each mode of sensibility Recent observations in both anatomical and physiological fields have, however cast grave doubt on the validity of this classical conception and, moreover suggest that nerve terminals in the skin have local functions to subserve apart from and in addition to their sensory function.

THE NEURO-ANATOMICAL PICTURE IN MAN

The anatomical picture is far more complex than has been supposed previously (Weddell 1945) and is thus more difficult to interpret but from the point of view of the dermatologist it supplies a more complex framework on which to base theories as to the mechanism of certain neurodermatoses which have been difficult to explain in the light of previous descriptions.

To determine the anatomy of tissue neural elements has proved an immensely difficult task chiefly for the reason that they are so difficult to display selectively in microscopical preparations without gross distortion

Weddell and Zander (1950) thought that phase contrast microscopy might help in the solution of this problem, for an analysis of the literature made it clear that there were almost as many descriptions of tissue neural elements as there were neurohistological techniques They found however that the only tissue which they could examine profitably in this respect was the cornea They thus carried out a detailed investigation into the neurohistology of the normal cornea as seen under phase contrast conditions, comparing and contrasting the pictures obtained in this way with those resulting from the use of the majority of other methods, currently used to display tissue neural elements. They found that phase contrast microscopy thus employed enabled them to give a more accurate and detailed description of the innervation of the cornea than had been given previously (Zander and Weddell 1951a) (Figs. 4 and 5) In addition the point which should be emphasized here is that, as a result of the work described in this paper and in a subsequent one (Weddell and Zander 1951) they were able to show in detail the nature of the artefacts produced by the various neurohistological techniques and also that artefacts can be produced by a number of other factors which include mechanical deformation the fixative employed, and so on This additional know ledge enabled them to carry out an experimental investigation into the reaction of corneal nerve fibres to injury using methylene blue staining and silver impregna

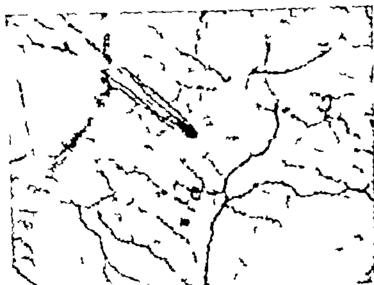


Fig. 4.—Fine, naked, axoplasmic filaments, ending among epidermal cells of a rabbit cornea. I centre of picture, stem fibre can be seen piercing Bowman's membrane and giving rise to profuse arborization of filaments, which are scattered over a wide area and intertwine with terminals derived from neighbouring stem nerve fibres (methylene blue preparation, 300).

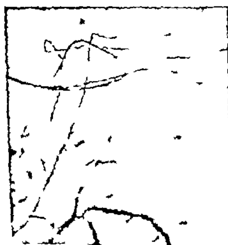


Fig. 5.—Fine, naked, axoplasmic filaments ending in *substantia propria* of rat cornea. Note large number of branches which arise from stem fibre, some of which pursue recurrent course (methylene blue preparation, 330).

tion for phase contrast microscopy was clearly of limited application in such an investigation (Zander and Weddell 1951b)

Following these observations and the improvements in technique which they had evolved in the course of their work investigations were made on the skin on the back of the human pinna in an attempt to correlate the results of sensory testing with the neurohistology of this region (Sinclair Weddell and Zander 1952). The ear was specially chosen because the skin over the dorsum has few structures separating it from the skin over the ventral surface, all of which can be examined neurohistologically under identical conditions for control purposes. Sensory testing showed that all the commonly accepted modalities of sensation can be recognized over the dorsum of the ear just about as well as on the front of the fore arm or over the finger pads. The skin is abundantly supplied with nerve fibres which before terminating, divide and subdivide repeatedly to form a complex cutaneous plexus Each nerve fibre branch then gives rise to a complex arborization of axoplasmic filaments which terminate, either in relation to hair follicles, or freely in the epidermis, dermis and around blood vessels No encapsulated nerve endings were seen in any position in the skin nor were there any in the cartilage nor in the skin of the ventral surface of the ear Incidentally this picture is exactly similar to that seen in skin from the dorsum of the rabbit ear

This investigation demonstrated among other things that encapsulated nerve endings of specific morphology do not subserve temperature sensibility in the human pinna In a succeeding publication, Hagen and her colleagues (1953) demonstrated that, in the human lip temperature sensibility is equally acute on either side of the red margin that is, in both hairy and glabrous skin No encapsulated nerve end-organs are seen in the hairy skin, but they abound in the mucous membrane in one and the same section. Hagen and her colleagues also pointed out the difficulty of classifying the encapsulated end-organs in glabrous skin on a morphological basis Incidentally they concluded from the samples of skin they had examined that encapsulated nerve endings are found only in glabrous skin. When this observation is taken in conjunction with the discovery that both encapsulated nerve end-organs and hair follicles have many points of detail in common, there is good justification for the belief that in glabrous skin encapsulated nerve end-organs replace and subserve the same functions as hairs that is to say they are activated by mechanical deformation

It has since been shown by Weddell and Pallie (1953a) that when improved histological methods are used employing the enzyme hyaluronidase, the nerves can be seen to terminate in the skin in a manner which so far has only been hinted at in the literature and which it has not previously been possible to demonstrate unequivocally

Briefly numerous nerve fibres reach the skin after branching and ramifying in the cutaneous nerve plexus These stem nerve fibres which are branches of parent fibres may be either myelinated or non myelinated but they are always surrounded by a sheath of Schwann cells. In some cases, myelinated fibres lose their myelin sheaths and travel for several millimetres as non myelinated fibres before giving rise to a profuse arborization of fine, freely ending, naked axoplasmic filaments. At the point of termination the filament is commonly somewhat enlarged. For the purposes of description it is possible to divide the terminals into three groups (1) unencapsulated nerve endings (2) endings related to hair follicles and (3) encapsulated nerve endings.

Unencapsulated nerve endings

The unencapsulated nerve endings are widespread and numerous but, when selectively represented by methylene blue or silver cannot be distinguished from one another on the basis of inherent morphological differences. They are found in different positions in the skin where their patterned arrangement is determined by the tissues in which they are situated, as will be explained in detail in the following paragraphs. It must be emphasized, however that it is not possible by casual inspection in normal skin to demarcate sharply the various sets of endings described, for they overlap and the filaments are numerous and intertwine closely

Epidermis

Ensheathed stem nerve fibres derived from the cutaneous plexus give rise to a profuse arborization of fine naked axoplasmic filaments which lie just beneath the basal layer of cells, giving rise at intervals to filaments which enter the epidermis to ramify among the cells of the *stratum germinativum*, where they terminate. A single stem axon, which may be myelinated when it springs from the cutaneous plexus, gives rise to a number of axoplasmic filaments which extend over a wide area of epidermis, the extent of the area depending upon the site from which the skin is obtained. In skin from the finger pad for instance, a stem fibre gives rise to filaments which extend over a surface area of a few square millimetres, whereas, in the forearm, they extend over an area greater than a square centimetre (Weddell, 1941). Filaments derived from neighbouring axons overlap and intertwine closely with one another No filaments enter the cytoplasm of the epidermal cells.

Dermis

Unencapsulated nerve endings are also found in the dermis. The fine naked axoplasmic filaments, which are derived in the same way from stem fibres springing from the cutaneous plexus, terminate among the cells, capillaries and connective tissue elements. They are scattered throughout the dermis and do not lie in constant relation to any particular tissue elements but are, nevertheless, most numerous where the capillaries are most abundant. Filaments derived from neighbouring *ensheathed* stem fibres overlap and intertwine closely with one another as they do just beneath the epidermis, but they are more widely scattered in depth so that it has not been possible to determine the relative extent of dermis subserved by the filaments derived from a single stem fibre.

Blood vessels and sweat glands

Terminals of similar morphology end in a comparable manner in relation to the walls of arteries, arterioles and venules. In the case of arteries, both myelinated and non-myelinated stem fibres have been seen. Finally we have been able to distinguish a similar series of terminals ending in relation to sweat glands.

Hair follicles

In the case of nerves ending in relation to hair follicles, stem nerve fibres approach the follicles from different directions like the spokes of a wheel. With regard to small hair follicles, only a few stem fibres are seen, but as regards large hair follicles, as many as 28 stem fibres, gathered into four or five bundles, have been counted. The parent fibres, which are myelinated and of large diameter reach the hair

follicles below the point at which the ducts of the sebaceous glands open into them. After giving rise to further collaterals each fibre ends in a profusion of fine, naked, freely ending axoplasmic filaments disposed in one of two planes The outermost layer of filaments is derived from parent fibres which lose their sheaths as they pierce the external layer of the dermic coat They lie among the collagen bundles in the middle layer of the dermic coat and encircle the hair in the form of a collar The innermost layer of filaments is derived from parent fibres which lose their sheaths as they pierce the vitreous layer The numerous fine, naked freely ending filaments ramify in a longitudinal direction among the cells of the outer root sheath (Fig. 6)

The size of the hairs and their follicles varies from place to place in different areas of skin In general the number of parent fibres and the wealth of the fila-

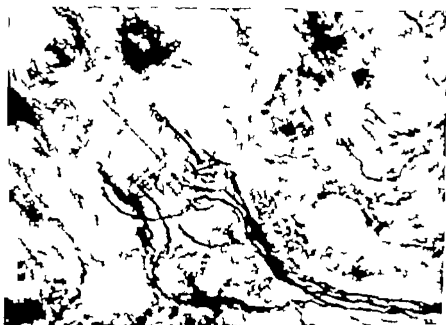


FIG 6.—Fine, naked axoplasmic filaments ending in relation to hair follicles in a rabbit ear Note numerous stem fibres supplying follicle containing thicker hair (methylene blue preparation, 350).

ments to which they give rise is directly related to the size of the hair follicle but not necessarily to the size of the hair During periods of active hair growth, however parts of the follicle appear disproportionately large.

Encapsulated endings

Encapsulated nerve endings were only seen in glabrous pieces of skin and in mucuous membranes. In one respect they can be said to take the place of the terminals around hair follicles for they are also aggregations of sharply circumscribed terminals subserved by ensheathed parent fibres of large diameter They vary in size, in shape and in situation from area to area in the same region and from region to region of the body A single encapsulated ending may be subserved by more than one parent nerve fibre and the course pursued by the stem axon

within the capsule may be relatively simple or extremely tortuous. In addition, the capsule may be thick and compact, or thin with the cells loosely grouped. It is impossible to classify these endings on morphological grounds owing to their remarkable diversity of form (Fig. 7). Despite this, however, the actual manner in which the nerves terminate is essentially similar in every case. An ensheathed stem axon is surmounted by a capsule of epithelial cells and connective-tissue fibres. The stem axons pursue a more or less tortuous course within the capsule and may branch repeatedly. Leaving the stem fibre or fibres at intervals along their course and at their terminations within the capsule, are a profusion of short, fine, naked axoplasmic filaments which branch repeatedly and terminate among the cells of the capsule. In some instances, a stem axon may pierce the capsule



FIG. 7.—Two encapsulated nerve endings of different shape in mucous membrane of a human glans clitoris. Note that stem fibres give rise to complex arborizations of naked axoplasmic filaments which end within the capsule (hyaluronidase-silver preparation, ×150).

and give rise to a series of fine, naked, axoplasmic filaments which terminate freely in the dermis or in relation to the epidermis.

In summary then, it can be said that all the nerve fibres which end in the skin ultimately give rise to a series of fine, naked, axoplasmic filaments which end in different zones. Neighbouring filaments are intimately related to one another and to the tissue elements among which they lie. Terminals from neighbouring nerves do not fuse with one another, however, nor have any axoplasmic filaments been seen to enter the cytoplasm of any cells with which they may come into relation.

It will be noted that these observations differ from those of Boeke (1940) and Stöhr (1928), to whom, however, credit is due for having pointed out the wealth of terminal nerve fibres which permeate various tissues. They differ in two important respects. In the first place, our observations do not suggest that the neuron theory should be abandoned from the anatomical point of view; on the contrary, the pattern of regeneration of nerve into the denervated cornea suggests

that each nerve fibre behaves in a highly specific manner reacting in an individual way to changes in its immediate environment (Zander and Weddell 1951b). *In the second place*, we have shown that both Boeke and Stöhr used techniques which necessarily give rise to artefacts and thus many of their observations are, we believe, misleading when used for the purpose of generalizing as to the detailed nature of the morphology of the peripheral nervous system (Weddell and Zander 1950) Nonidez (1936) has also criticized the work of Boeke and Stöhr on parallel grounds

EXPERIMENTAL OBSERVATIONS IN ANIMALS

We must now discuss the implication of certain investigations in animals with regard to the mechanism of cutaneous sensibility in man Weddell and Pallie (1953c) have just concluded a comprehensive survey of the pattern of the distribution and innervation of the hairs on the dorsum of the rabbit ear Briefly they have demonstrated that the hairs are arranged in a complicated pattern of lines and loops which can be seen clearly with a hand lens after clipping the hairs. The hairs forming the pattern are clustered in groups of three, five and eight hairs but there are occasional *single hairs present. The hairs vary in length and diameter* and in the angle which they make with the plane of the skin where they emerge. Commonly one hair in a group is larger than the others and measurements of the distances between individual hairs and groups of hairs varies from place to place in a random manner These observations suggest that any given area of skin from the dorsum of the rabbit ear has certain unique characteristics and thus differs from any other given area. This is indeed what might have been expected for it has been shown that the distinctive skin ridges on the finger pads in man, even in identical twins, are arranged in unique patterns which are beyond the control of heredity (Gates, 1946)

In addition to this, Weddell and Pallie have shown that the larger the hair the *more and of larger diameter are the myelinated nerve fibres supplying the follicle.* The nerves supplying the hairs reach them from three main groups of nerve bundles which enter the base of the ear The great majority of myelinated dorsal root fibres do not give rise to *collaterals until the bundles in the ear enter the cutaneous* nerve plexus where they branch repeatedly to cover a wide area to supply numerous hairs. Overall counts have shown that there are approximately five times as many hairs as there are dorsal root nerve fibres supplying the skin over the back of the rabbit ear

Weddell and Taylor (1953) using an evoked action potential technique, have shown that every hair is supplied by at least two dorsal root nerve fibres, many large hairs receiving as many as eight fibres Similar observations have been made in the case of other animals (Kuhn, 1953)

Finally degeneration experiments have shown that axons, whose terminals subserve hairs distributed over a given area of skin are arranged in a completely *random manner in relation to one another* In other words any incomplete random injury inflicted on the nerve trunks approaching the dorsum of the ear will tend to give rise to a uniform sensory loss throughout the given area and not to isolated patches of *anaesthetic skin.*

Thus, in the case of the rabbit ear not only is it impossible to send nerve im

pulses up a single myelinated nerve fibre by stimulating a single hair by natural means, but, which is of even greater importance, it is not possible to calculate the effect of a stimulus on a hair in terms of action potentials without knowing the force used to stimulate, the place of stimulation and the temporal aspect of the stimulus, together with a complete analysis of the physical properties of the hair the hair follicle and the skin surrounding it.

To sum up in the case of the dorsum of the rabbit ear a given stimulus activating the hairs will probably throw a unique pattern (in number time and space) of action potentials on to the spinal cord, each time it is applied to different areas of skin, however close these areas are to one another

EXPERIMENTAL OBSERVATIONS IN MAN

There is no reason to believe that the patterned arrangement of the nerve terminals in the skin is any less complicated in man than in the rabbit and, in fact, it is almost certain that it is more complicated. For this reason, any theory of cutaneous sensibility cannot afford to ignore the possible modifying effect of the pattern of impulses aroused on the reaction evoked and on the modality perceived. The work of Lele, Sinclair and Weddell (1953) and Lele, Williams and Weddell (1953) serves to emphasize this point. Lele Sinclair and Weddell have shown that the reaction time to touch varies inversely both as the log. of the area stimulated and the log. of the magnitude of the force applied In addition, they have shown that reaction time probably varies directly with the threshold to touch of the area stimulated.

Lele, Williams and Weddell have shown that the same thing is true of a radiant heat stimulus, but they have also shown that the perception aroused varies according to the number of nerve fibres activated by the same stimulus. In other words, it now appears unlikely that the statement that different parts of the sensory pathway have components specific for each mode of sensibility is correct. That is not to say that some kind of segregation of nerve fibres on a modality basis does not occur in the spinal cord. There is clinical evidence that some sort of segregation (Brown-Séquard syndrome) does exist, but it implies that the conception of one ending, one nerve fibre, one pathway one perception, based on the absolute validity of the law of specific irritability can no longer be regarded as a sound working hypothesis

From the dermatologist's point of view perhaps the most interesting recent discovery is related to the fine, naked, axoplasmic extensions which abound in the skin.

LOCAL FUNCTION OF NERVE TERMINALS

In a paper on the innervation of cutaneous blood vessels in the rabbit ear Weddell and Pallie (1953b) have shown that, as is the case elsewhere in the skin, the vascular nerves can be regarded as consisting of two morphologically distinct components stem nerve fibres and terminals. The stem nerve fibres reach the arterioles and venules directly from the cutaneous plexus. They reach the vessels in bundles of four to six fibres and proceed to run close to and parallel to the vessel for some distance. At intervals, off-shoots from stem nerve fibres give rise to numerous fine, naked, axoplasmic filaments which terminate freely in slight

that each nerve fibre behaves in a highly specific manner reacting in an individual way to changes in its immediate environment (Zander and Weddell, 1951b). In the second place, we have shown that both Boeke and Stöhr used techniques which necessarily give rise to artefacts and thus many of their observations are, we believe misleading when used for the purpose of generalizing as to the detailed nature of the morphology of the peripheral nervous system (Weddell and Zander 1950) Nonidez (1936) has also criticized the work of Boeke and Stöhr on parallel grounds.

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Thus in the case of the rabbit ear not only is it impossible to send nerve im

behaviour There is, in fact, indirect physiological evidence that there is, for Alvarez Buylla and Ramirez de Arellano (1953) and Gray and Sato (1953) have shown that mechanical stimuli of low amplitude evoke no response in the parent nerve fibre of a pacinian corpuscle. When the amplitude is increased, a local response can be recorded up to 4 millimetres from the corpuscle. The amplitude of the response increases smoothly with the amplitude of the stimulus until at threshold a propagated disturbance emerges from the late part of the local potential. Now the stem nerve supplying a pacinian corpuscle gives rise to a series of fine naked, freely ending, axoplasmic filaments, which end within the wall of the corpuscle in the same way as stem nerve fibres give rise to terminals ending in relation to arterioles and capillaries (Weddell and Pallie, 1953b). It is thus tempting to conclude that a similar mechanism obtains in each case.

Assuming this to be true, a morphological basis for the so-called "nocifensor" system of nerve fibres (Lewis, 1942) no longer presents an apparently insoluble problem. It will be remembered that Lewis's observations suggested that there was a dorsal root efferent system of nerve fibres which formed a continuous net work just beneath the epidermis and which was associated, among other things, with the spread of flare and with hyperalgesia. Lewis argued that this system was independent of the sensory systems of "pain" nerves, for nocifensor reactions are not necessarily accompanied by the sensation of pain. Woollard, Weddell and Harpman (1940), on the other hand, demonstrated the presence of hyperalgesia in an area of skin from which only pain could be evoked and which was subserved by terminals from a single stem nerve fibre

If the hypothesis that nerve terminals only give rise to local responses when stimulated is acceptable, it is possible to harmonize these apparently divergent points of view The terminals ending in relation to the capillaries are so disposed that local responses (resulting from stimuli involving short segments of superficially situated neighbouring terminals) can easily spread far enough in the arborization of axoplasmic filaments to produce a flare without necessarily extending all the way to the stem fibres which they subserve. Nerve terminals functioning in this manner could be said to constitute an independent physiological system, which would accord with Lewis's conception of a nocifensor system behaving independently of the sensory system of pain nerves.

The association of hyperalgesia with the nocifensor system strengthens our hypothesis for the presence of flare and would suggest that only the slightest additional stimulus would be necessary to build up the strength of the local response sufficiently for it to initiate a propagated action potential in the parent pain nerve fibre. It is, of course, assumed that the local response is connected with chemical changes concerned in the release of substances which influence the state of the capillaries.

If the interpretations made here concerning the nocifensor system are correct, the functional significance of the terminals ending in relation to the arterioles and elsewhere in the skin may be greater than is usually supposed and would strengthen the arguments of those who still believe that sensory nerves have "trophic" functions in the skin. Whether or not antidromic impulses flow from the spinal cord down sensory nerves under physiological conditions is not known, but Holton and Holton (1952) and Holton (1953) have recently brought forward indirect biochemical evidence in favour of this notion.

enlargements on the surface of the smooth muscle fibres the stem nerve fibres themselves end in a similar manner Axoplasmic filaments from neighbouring parent fibres overlap and intertwine so closely with one another that, at low magnifications, the terminals have the appearance of a continuous nerve net (Fig. 8). Nerves are not seen to end in any constant relationship to capillaries. Nevertheless, capillaries are surrounded by the numerous nerve terminals which end in relation to the epidermis and tissues of the dermis, including those which emerge from encapsulated nerve endings Axoplasmic filaments sometimes terminate on the surface of the capillary walls but, more commonly in their close neighbourhood, for they cannot be said to end in a constant relationship to any particular structural component of the dermis nor to any particular part of such a component, although a greater number of filaments and terminals are seen where capillaries are most abundant

The terminals derived from stem fibres subserving encapsulated nerve endings, which terminate in close relation to capillaries are of interest for they correspond



FIG 8.—Fine axoplasmic filaments on surface of a small arteriole in a rabbit ear (hyaluronidase methylene blue preparation, 650)

loosely to the pictures commonly seen in physiological text books illustrating the mechanism of the axon reflex The difficulty of tracing the branching nerve fibres accurately throughout their ramifications in the cutaneous nerve plexus has prevented us from demonstrating the morphological basis of axon reflexes in which the response to a stimulus occurs at a distant site. The existence of such pathways has been demonstrated physiologically by Adrian Cattell and Hoagland (1931)

Following complete removal of the cervical sympathetic chain no degenerating nerve fibres were seen in relation to capillaries in the dorsum of the rabbit ear but a number of degenerating fibres, with normal nerve fibres, were seen in the walls of arterioles and venules These experiments, while not conclusive, suggest that the nerve fibres which influence capillaries come from somatic sources, whilst those supplying arterioles and venules come from both autonomic and somatic sources.

The morphological contrast between the stem fibres and the fine axoplasmic terminals suggests that there may be some difference in their physiological

CHAPTER 4

PHYSIOLOGY AND FUNCTIONAL PATHOLOGY OF THE SKIN

G R. CAMERON AND W G SPECTOR

SINCE the first edition of this book appeared the main advances in this sphere have been made in the study of the reaction of the skin to injury in its widest sense, including antibody production, the response of the skin to hormonal influences and in our knowledge of the structure and function of collagen, elastic tissue and ground substance, and of sweat glands and sebaceous glands.

REACTION OF THE SKIN TO INJURY

Dermatology is fortunate in that the accessibility of the skin has made it the chief tissue in which the experimental study of inflammation is now carried out. Recent work on this subject can be classified as being primarily concerned with (1) substances which may mediate the changes seen in inflammation, for example, histamine and peptides, (2) spreading factors and (3) the influence of cortisone and other hormones.

Substances which may mediate inflammatory changes

Histamine

Of compounds with an action on the skin resembling the effects of inflammation, histamine is the best known. Interest in its ability to cause pain as shown by the work of Lewis has recently been revived by Rosenthal (1950), who injected histamine into the skin and observed an immediate and a latent painful sensation.

The major advance in the study of the part that histamine may play in local reaction to injury however has come about by study of histamine liberation. It has long been known that many organic bases cause liberation of histamine into the bloodstream when introduced into animals. The introduction of perfusion techniques for isolated skin has now made possible the direct demonstration of histamine liberation from this tissue by a variety of compounds (Feldberg and Paton, 1951). These substances include Propamidine, δ-tubo-curarine, morphine, codeine and apomorphine. The most powerful is a complex compound known as 48/80 1 molecule of which liberates about 80 molecules of histamine from skin. This release is "explosive" in character the liberated histamine then being washed out of the skin by the perfusion fluid. Histamine release is also brought about by horse serum in non-sensitized cats and sensitized dogs (Feldberg and Shachter 1952). Here at least in some cases, the release is not explosive, but more prolonged. The phenomenon of histamine release is not accompanied by any histological evidence of damage to cells or extracellular structures.

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Peptides

Work by Menkin (1936) Duthie and Chain (1939) and Cullumbine and Rydon (1946) established that several enzyme digests of proteins had the property of increasing vessel permeability in skin when injected into this tissue Later work (Spector 1951) confirmed that the active principle of these digests was a peptide and showed that the crystalline peptide pancreatic trypsin inhibitor (molecular weight 6 000) had a similar effect on vessel permeability In a peptic digest of fibrin it was found that this biological property was shared by peptide molecules whose average chain length varied from 8 to 14 amino-acid residues. Strong evidence exists that the property of increasing vessel permeability in skin resides not in one but in large numbers of peptides above a certain molecular size.

The hypothesis underlying this work is that dermal injuries of different types, whose only common element is destruction of tissue, could lead to the changes of inflammation by causing peptides to be liberated in the skin. Proteolytic enzymes exist in the skin as well as in blood capable of degrading tissue proteins to peptides (Cullumbine and Rydon 1946) Work by Moon and Terschacovec (1951) suggests that soluble proteins extracted from minced normal tissues may have an effect similar to that of peptides on vessel permeability These proteins could, however be proteolytic enzymes as discussed above.

The possibility that peptides increase the permeability of skin vessels by causing the liberation of histamine from cells is now being widely considered. Direct evidence of this is not yet forthcoming, but work by Miles and Miles (1952) provides some support for such a view

All peptide fractions so far shown to increase capillary permeability cause the emigration of polymorph leucocytes from blood vessels into the site of injection This property is shared by in addition a low molecular weight group without demonstrable effect on vessel permeability (Spector 1951) The nature of the effect so exerted on leucocytes is unknown, the most popular view being that it is chemotactic, that is a directional influence on the polymorphs themselves. Ability or inability to demonstrate this *in vitro* has varied with the methods used The most recent and theoretically most sound technique has failed to show a true chemotactic effect of protein digests on polymorphs. These experiments, however have also revealed other discrepancies between the leucotactic properties of compounds *in vitro* and in the intact skin (Harris, 1953)

Spreading factors

The dermis and subcutaneous tissues act as a partial barrier to the spread of fluid and particulate matter through them The barrier is believed to be due largely to a gel, comprising the ground substance of these tissues, and composed mainly of hyaluronate and partly of chondroitin sulphate, both in varying degrees of combination with protein (Meyer and Rapport, 1952)

Hyaluronic acid is a high molecular weight straight-chain polymer of a disaccharide composed of N-acetyl glucosamine and glucuronic acid in equimolecular amounts. In some other tissues the predominant mucopolysaccharide of the ground substance is a different compound. Thus in cartilage it is chondroitin sulphate.

Spreading factors fall into three groups (a) enzymes whose substrate is hyaluronate and other polysaccharides that is the hyaluronidases, (b) substances degrad

ing hyaluronate non-enzymatically and (c) spreading factors with no demonstrable effect on hyaluronate.

Hyaluronidases

These enzymes are of very widespread distribution in nature. Besides being present in many animal tissues, particularly in testis hyaluronidase is also found in many micro-organisms including some streptococci, staphylococci, pneumococci *Clostridia welchii* and in a non-virulent strain of *Treponema pallidum* (Hussey and Nowinski, 1949). There is general agreement that hyaluronidase can be demonstrated in skin only after autolysis (Meyer and his colleagues 1941). No hyaluronidase has yet been fully purified.

All hyaluronidases appear to act in a similar fashion. Their site of action is believed to be confined to the glucosaminidic bonds. As a result of enzymic rupture of these linkages the hyaluronate molecule becomes first depolymerized and then hydrolysed to diffusible products with liberation of reducing sugar and of the aldehydic group of the N-acetyl glucosamine residues. There is strong evidence that hyaluronidase, at least from the testis, first attacks hyaluronate near the centre of the polysaccharide chains and does not hydrolyse its substrate all the way down to monosaccharides (Meyer and Rapport, 1952).

The increase in rate of spread of solutions and suspensions through the skin when hyaluronidase is added to the injection fluid is believed to be due to the enzyme's effects on the physical properties of hyaluronic acid. These effects consist of a reduction in viscosity becoming more pronounced the more the reaction proceeds to complete hydrolysis, a loss of the ability to precipitate proteins and a loss of fibrous clot formation with proteins in acid solution.

Loss of viscosity of the dermal and subcutaneous ground substance is presumably the main operative factor in the spreading effect of hyaluronidase. There is some evidence that the enzyme has little influence on rapidity of diffusion unless the test solution is injected into the skin so as to raise a bleb and thereby increase the interstitial-fluid pressure (Hechter 1947). This finding may be related to the fact that a relatively dilute gel such as dermal ground substance should have little effect on the rate of diffusion of small particles through it. If the particles were introduced into the gel as a solution injected under pressure, however the viscosity of the gel might become a limiting factor

It would seem that the spreading effect of hyaluronidase is not entirely due to the depolymerization of hyaluronate. This is suggested by the inhibition of its spreading effect *in vivo* by antihistamines, compounds which have no inhibitory influence on the degradation of hyaluronate by hyaluronidase *in vitro* (Elster Freeman and Lowry 1949). The most likely explanation of this is that the injection of hyaluronidase into the skin helps to further an inflammatory response with consequent increased rate of disposal of injected solutions. Purified hyaluronidase itself has been shown to be without effect on capillary permeability (Zweifach and Chambers, 1950).

Any part that hyaluronidase plays in inflammatory lesions of the skin is still conjectural. In infections the enzyme could facilitate the passage of organisms through the tissue. There is, however no apparent connexion between the presence of hyaluronidase in a given strain of micro-organisms and the virulence of the strain. A sequence of events in the skin might be associated with liberation

of hyaluronidase. This enzyme could then break down ground substance with a resultant spreading effect just as liberation of proteolytic enzymes by similar tissue damage may enable peptides to be formed which increase vessel permeability and induce emigration of leucocytes.

Non-enzymatic degradation of hyaluronate

A variety of agencies simulate the effect of hyaluronidase in that they reduce the viscosity and protein precipitating ability of hyaluronic acid. These agents include oxidized ascorbic acid (Skanse and Sundblad 1943) x rays and azo compounds (McClean and Hale 1941), ultrasonic waves (Hunzinger Süllmann and Viollier 1949) and heavy metals (Jensen, 1949) In addition to the changes in physical properties they effect on hyaluronic acid the agencies, like hyaluronidase, lead to the formation of low molecular weight diffusible products. Unlike the enzyme however such agents do not cause reducing groups to be liberated

Many of these agents such as oxidized ascorbic acid and azo compounds are known to have a spreading effect when injected into skin. They differ from hyaluronidase however in that they exert their effect only on the skin of living animals, the enzyme being active on both live and dead skin.

Spreading factors without demonstrable effect on hyaluronate

A large group of compounds exist which cause a spreading reaction when injected into living skin but which have no detectable effect on the chemical or physical properties of hyaluronic acid These compounds include bacterial products, "peptone" preparations, lecithin, kallikrein glycerol urethane and arsenical and organic mercurial compounds (Hechter 1950) It is possible that these compounds act by liberating or activating skin hyaluronidase (Hobby and his colleagues, 1941). Since, however all the substances share the ability to induce an inflammatory reaction it is more likely that their spreading effect is related to this property One way in which an inflammatory response could cause a spreading effect is by the liberation of proteolytic enzymes postulated earlier Hyaluronic acid in skin like other mucopolysaccharides, occurs partly as protein complexes and these might be broken down by such enzymes

Effect of hormones on reaction of skin to injury

It is now well known that cortisone delays wound healing in the skin of humans and many animals (Ragan, and his colleagues, 1949 a and b) The drug appears to do this by depressing fibroblastic and angioblastic activity and by reducing the amount of ground substance and collagen fibres and by delaying the re-absorption of extravasated blood Following the administration of cortisone, granulation tissue formation is absent or deficient and the tensile strength of scars is reduced Sex hormones and hypophysectomy also retard wound healing in the skin On the other hand, pituitary growth hormone thyroxine and desoxycorticosterone, stimulate the formation of fibrous tissue (Taubenhaus and Amromin, 1950). Although the extent of the effect of cortisone on wound healing in the skin varies with dosage and animal species, this action has been obtained in all species investigated, including man (Baxter and his colleagues, 1951)

Cortisone also affects the earlier phases of inflammation particularly the forma-

tion of a fluid and cellular exudate. The drug reduces the extent of this exudate and diminishes the amount of oedema fluid and fibrin and the number of poly morphs, lymphocytes and mononuclear cells in traumatized inflamed skin (Spain, Molomut and Haber 1950). Cortisone has a similar effect in dermal inflammation induced by anaphylaxis (Shwartzman, Schneierson and Soffer 1950).

The suppression of inflammatory symptoms by cortisone for example in rheumatoid arthritis, is known to take some days to develop In the rat the effect of the drug on the formation of inflammatory exudate in the skin has been shown not to be demonstrable until 48 hours after the injury even though the animals were fully pretreated with cortisone (Lattes and his colleagues, 1953). This could mean that the different phases of inflammation are mediated by more than one liberated compound or mechanism, some inhibited by cortisone and others not. Alternatively such a result might be explained by a progressive weakening of only one inflammatory stimulus with the passage of time, the stimulus being partially inhibited by cortisone.

Cortisone depresses or abolishes the increased permeability of skin vessels induced in rabbits by histamine and certain peptides (Bangham, 1951). The drug also lowers the protein concentration in the fluid within inflammatory blisters. Effects of this kind seem likely to explain the reduction of fluid and fibrin exudate by cortisone. No *in vitro* action of cortisone on polymorphonuclear leucocytes has been demonstrated although the drug appears to destroy lymphocytes in tissue culture (Trowell, 1953).

Cortisone increases excretion of non-protein nitrogen and may therefore cause protein breakdown. It is possible, then, that the drug's effect on ground substance and collagen in skin may be due to a reduction in net synthesis of protein molecules in these constituents of skin (Clark, 1950). With regard to ground substance, cortisone has been found to inhibit the synthesis of chondroitin sulphate, a connective tissue polysaccharide, by wound tissues *in vitro* (Layton, 1951). Again, the ground substance of skin wounds in animals treated with cortisone shows less metachromasia than in controls (Lattes and his colleagues, 1953). Metachromasia is an index of polymerization which in turn should vary directly with net synthesis of ground substance polysaccharide. In view of this it may seem surprising that cortisone inhibits the spreading action of hyaluronidase (Opsahl, 1949), since hyaluronidase itself leads to depolymerization of ground substance. The answer may be that cortisone diminishes the effect of hyaluronidase in the way that antihistamines do or alternatively that it does not directly lead to depolymerization but rather inhibits synthesis of polysaccharide, breakdown meanwhile proceeding at the normal rate.

Absorption through the skin

Little evidence has appeared of late to challenge the importance of the partition coefficient of compounds, that is, their solubility in oil relative to that in water in determining their absorption into the skin. With regard to the effect of vehicles, polyethylene glycol (Carbowax) has been found to promote the absorption of sulphonamide into injured skin particularly if the vehicle was not combined with oil or water bases. Extending the time of application and increasing the concentration failed to promote absorption further (Clark, 1946). Similarly an irregular absorption of adrenaline, penicillin and acetylcholine when

dissolved in diethylene glycol monoethyl ether has been found for the skin of rabbits (*Luduena Fellows and Driver 1948*)

In respect of percutaneous absorption of heavy metals a high absorption of tetraethyl lead and a low absorption of lead oleate, arsenate and acetate has been observed with increased absorption after mechanical injury to the skin (Lang and his colleagues, 1947) The same authors observed that the cutaneous absorption of mercury was reduced if excess of ointment was removed and increased if the inunction site was covered

There is general agreement that injury to the skin facilitates percutaneous absorption This has been demonstrated for example, in toxic and allergic dermatoses (Seeberg 1947) and with the aid of radon in leg ulcers (Lange and Evans, 1947). By using radioactive phosphorus variation in percutaneous absorption has been demonstrated with different phases of the menstrual cycle, absorption varying inversely with skin reactivity (Seeberg, 1950)

Effect of hormones on hair growth

Hair growth has been suppressed in male rats by adrenal cortex preparations (Baker and Whitaker 1948) and in female rats by a combination of oestrogen administration and oophorectomy (Baker and Whitaker *1949) This effect was* abolished by adrenalectomy Adrenalectomy has also been found to cause accelerated cycles of hair growth in Norway rats (Dieke, 1948) Cortisone, whole adrenal extract and compound F when applied locally to the skin stop hair growth and decrease sebaceous activity in both sexes, the skin eventually becoming refractory (Castor and Baker 1950) On the other hand cortisone has been reported as having a stimulating effect on hair growth in patients with alopecia.

COLLAGEN

This important material exists within the dermis of the skin as a fibrillar glucoprotein and part of a complex network of bands and membranes. Its physical properties have recently been reviewed by Gross and Schmitt (1948) Cameron (1952) and Randall and his colleagues (1952)

It will be recalled that collagen fibres (Figs. 9 and 10) are built up from amino acids joined in series by means of peptide bonds to form long polypeptide chains. Astbury (1940) suggested that the order of arrangement between the component amino acid residues is –P–G–R– over a substantial part of the chain length, P being proline or hydroxyproline, G glycine R one or other of the remaining amino acids known to be present in collagen Pauling and Corey (1952) favour a spiral *configuration of the chains which are united laterally to their neighbours by hydro*gen bonds, salt linkages and van der Waal s forces to produce polypeptide grids or sheets, the distance between the parallel chains or spirals being 10–12 A depending on *the state of hydration Grids are piled one upon another at distances of* 4 5 A being united along the chain backbones by hydrogen bonds to produce the collagen crystallites. Collagen fibrils are built up by lateral and end-to-end aggregations of the crystallites *(Lloyd and Garrod 1946 Bear 1952)*

Procollagen has been recently described by Russian workers as a substance that can be extracted by soaking mammalian skin in citrate buffer *p*H 4 It resembles collagen in amino *acid composition and yields gelatin on boiling Dialysing* solu

tions against distilled water results in the precipitation of fibres. Electron microscopic studies show up differences between procollagen and collagen fibres (Highberger Gross and Schmitt, 1951). Apparently there is a slow turnover of collagen in tissues but the precise relationship to procollagen is not yet understood, (Neuberger Perone and Slack, 1951 Neuberger 1952) The physical properties of collagen may vary too, from tissue to tissue (Banga, Balo and Novotny 1948–9). Obviously all such studies may have a profound bearing on the physiology of the skin and may throw light on many problems of dermatology

The long-continued dispute about the origin of collagen from, or in connexion with, fibrous tissue cells goes on continually and it has not yet been decided whether



FIG 9.—Electron-photomicrograph of unmodified collagen fibres from the leg of fowl 'Cleaned' in saline Shadowed with Pd-Au. Magnification 28,000. *(By courtesy of Prof J T Randall F.R.S., and Dr A V W Martin, Medical Research Council Biophysics Research Unit King' College London.)*

the fibroblast buds off the collagen fibre or secretes something which then unites with intercellular material at a little distance from the cell to form the fibril. Bartsell's view (1915) that fibrin is transformed into collagen has not met with favour The discovery of a characteristic periodicity in the electron microscopic pictures of collagen fibrils has introduced precision into the identification of these fibrils and by means of such methods Porter and Vanamee (1949) have demonstrated the collagenous nature of fibres formed in tissue culture, presumably but not certainly by fibroblasts.

New studies of wound healing in scorbutic guinea-pigs have shown the importance of homogeneous ground substance for the formation of collagen (Penney and

Balfour 1949 Gersh and Catchpole, 1949) Without the one, the other does not differentiate completely or may be missing

We are still in the dark about the chemical interrelationships. The ground substance of cartilage, for long thought to be a derivative of fibrous tissue, has recently been studied by Partridge (1948) who maintains that it consists of chondroitin sulphuric acid in association with disordered collagen. A complex union occurs *in vitro* between chondroitin H_2SO_4 and the proteins of chondromucoid at hydrogen ion concentrations within the physiological range. Partridge suggests that the strongly acid sulphate groups of chondroitin H_2SO_4 are probably held in



FIG. 10 —Electron-photomicrograph of collagen fibres from tendon of human hand (biopsy specimen). Cleaned in saline for 3 days, fixed in 70 per cent alcohol and stained with PTA. Magnification 38,000 (*By courtesy of Prof J T Randall F.R.S and Dr A J B Martin Medical Research Council Biophysics Research Unit King's College London.*)

combination with the basic residues of the protein the net charge of the complex being adjusted mainly by a competition between alkaline metal and hydrogen ions for carboxylic acid residues in both protein and mucopolysaccharide. He also suggests that the intercellular elements of connective tissue may be thought of as a network of collagen fibrils, in some places organized into parallel bundles to form microscopic fibres, elsewhere relatively disorganized and heavily cross-linked by association with chondroitin H_2SO_4 Partridge thinks that the latter compound may act as a multivalent anion and cement together the protein molecules to form fibrous macromolecules and eventually fibre bundles. Other workers,

notably Blix and Snellman (1944) and Bunting (1950) have drawn attention to the concentration of sulphated mucopolysaccharides in skin and especially in relation to hair follicles.

Fresh evidence is coming to light about the mode of action of hormones on the formation of collagen and it may eventually clarify the relationship of such fibrils to ground substance. The complicated skin responses in the circumgenital region of monkeys to oestrogens is discussed by Zuckerman (1940). Recent work on the adrenals shows that desoxycorticosterone, a product of the adrenal cortex, stimulates fibroblasts and encourages collagen formation around sterile abscesses whereas testosterone and oestradiol inhibit the fibroblastic production of collagen (Taubenhaus and Amromin, 1949). Several groups of workers have now established the retarding action of cortisone on experimental wound healing and the healing of biopsy wounds (Colston Symposium 1953). Evidence associating hormones with the intercellular ground substance is also accumulating from various sources. The nature of this ground substance is discussed elsewhere so that we need only recall the depolymerizing action of hyaluronidase and the testis spreading factor the antagonistic action of luteinizing and follicular hormones upon the spreading of dyes in the skin (Sprunt and McDearman, 1940) and the inhibition of hyaluronidase which has been claimed by several workers though not confirmed by others. Injection of testosterone into newborn chicks accelerates the formation of metachromatic ground substance, that is, mucopolysaccharides in the comb (Ludwig, Boas and Soffer 1950) but oestrogen, adrenal cortex extract and cortisone apparently were without effect. There is some reason to associate a thyroid hormone with the deposition of mucopolysaccharides (Ogston, Philpot and Zuckman, 1939 Boas and Soffer 1950 Watson and Pearce, 1947 and 1949) but the intermediate stages of this mechanism are not known. No doubt these observations have some bearing on the pathology of collagen, especially the so-called "collagen diseases and the reader is referred to the stimulating article by Klemperer (1950) for further suggestions.

ELASTIC TISSUE

The earlier literature on the elastic tissue of the skin is fully reviewed by Hass (1939), who insists that elastic fibres are always associated with collagen fibres. More recently Dick (1947) has examined the character and arrangement of the elastic tissue in skin over almost the whole human body and has made some observations on oedematous skin. He finds that elastic tissue in the normal skin consists of a superficial subepidermal plexus of fine fibres and of a deeper layer of much larger fibres. The latter seem to be the more important in connexion with the physical property of elasticity in the skin. Little variation occurs in quantity and arrangement of elastic tissue in the same area of *different* individuals except in the age-groups of 15–40 years. That of the eyebrows is especially subject to degenerative change with advancing age. Banks of connective tissue consisting of collagen and elastic fibres run throughout the subcutaneous fat and allow of considerable range of movement of the skin. In the palm and sole, however subcutaneous fat is largely replaced by dense white fibres binding the skin firmly to the deep tissues. Such an arrangement prevents the development of oedema in these locations. In skin which is wrinkled and pigmented, as in parts exposed to

the weather the elastic tissue is increased in amount and irregularly distributed, being condensed into large solid masses superficially though the fibres remain separate in the deeper parts With generalized oedema separation of the fibres sets in and as the oedema becomes long standing the large elastic fibres shorten and break up often to a marked degree The fine subepidermal plexus is usually little altered but lies much deeper to the epidermis than in a normal case, suggesting that the loose areolar tissue immediately below the epidermis collects more fluid in oedema than the denser part with the main white and yellow elastic fibres.

THE SWEAT GLANDS

Although the sweat glands have been studied for many years by means of histological and physiological methods there are still gaps in our knowledge about their structure and function A typical sweat gland is composed of three distinct portions (1) the glomerulus, which lies deeply within the dermis or subcutis and consists of a coiled tubule which secretes much of the sweat, (2) the duct of the sweat gland which passes through the *stratum corneum* as a tight spiral, and (3) the adnexa of the sweat gland, often called the fibrillar bodies or myo-epithelial elements. Recent studies of the sweat glands in the cat and rabbit by Sperling and Koppanyi (1949) indicate a more complex method of production of sweat than was formerly realized These workers made use of the observation that active sweat glands prevent neutral leuco methylene blue from turning blue in the presence of molecular oxygen while inactive glands become stained In this way they could follow the changes accompanying sweating in histological preparations. Amongst their most interesting findings was the discovery that the adnexa shrink when sweat is produced and expand during anhidrosis. They suggest that shrinking indicates loss of water which may contribute to the initial outflow of sweat

At the same time, the portion of the duct in the *stratum corneum* changes from a tight spiral to a loosely twisted tube and ampullae appear at irregularly spaced intervals, suggesting that the outflow of sweat goes on in a succession of droplets. Hence sweating seems to involve at least two possibly three, sources, all reacting to the same stimuli at the same time (a) the myo-epithelial elements, (b) the glomerulus of the sweat gland proper and (c) the proximal portion of the duct of the gland These components apparently have the same innervation since cholinotropic drugs induce changes in glomerular function and in the appearance of the myo-epithelial elements simultaneously

There is general agreement that sweat seems to be more than an ultrafiltrate for sweat pressures of 250 millimetres of water have been reported in a single duct of a gland (Best and Taylor 1945). However the composition of sweat indicates that part of it must be an ultrafiltrate, for (a) there are no constituents in sweat which do not occur in the blood, (b) the reaction of duct sweat like that of the blood is slightly alkaline and (c) various substances such as bromides and iodides when circulating in the blood can be recovered from the sweat. When men perspire heavily as the result of exercise in a hot, humid atmosphere, salt is transferred from the extracellular to the intracellular compartments of the body if the salt losses during sweating are not replaced (Ladell 1949). The immediate source of the water lost at the same time is the extracellular fluid which also provides the chloride and this may lead to a greater or less disturbance of osmotic

equilibrium between the extracellular and intracellular compartments. Ladell finds that such disturbances do not develop to any great extent, for the equilibrium is quickly restored by simple fluid transfer: when chloride is not replaced water flows from the extracellular to the intracellular compartments until osmotic equilibrium is re-established.

However when a healthy man becomes acclimatized to heat, electrolytes are reabsorbed from the sweat glands and the tubules of the kidneys, through the influence of increased adrenal cortical activity (Conn and his colleagues, 1948). With restricted ingestion of sodium chloride, a positive balance of sodium chloride is maintained only by reabsorption from the sweat, the effect of the sharply increased adrenal cortical activity which develops under such conditions lasting for a much shorter time upon reabsorption from the renal tubules than on the sweat glands. These observations serve to show the fine balance that is maintained through homeostatic controlling mechanisms, between the body fluids and the sweat.

Some years ago Takahara (quoted by Kuno, 1934) estimated that from 0·003 to 0·005 milligram of fluid is discharged during 12–30 seconds when a palmar sweat gland becomes active. Improved estimations by Randall and McClure (1950) have been made on the amount of sweat excreted from different areas of the skin which together with sweat counts by means of the iodine-starch-paper method of Randall allows the average output of sweat per gland under various conditions to be calculated. Such studies have shown that the output on the arms and legs is greater than on the dorsal surfaces of the hand and foot similar differences were observed when the sweat glands were stimulated by the introduction of mecholyl into the skin by ion transfer Some of Randall and McClure's figures are given below

Normal sweating in a warm environment (means)

Upper arm	0·0037 mg./sq	cm./min.
Forearm	0·0043	,,	,,
Dorsum of hand	0·0031	,,	,,
Thigh	0·0040	,,	,,
Leg	0·0042	,,	,,
Dorsum of foot	0·0021	,,	,,

Sweating after mecholyl (means)

Upper arm	0·0067 mg./sq	cm./min.
Forearm	0·0057	,,	,,
Dorsum of hand	0·0044	,,	,,
Thigh	0·0071	,,	,,
Leg	0·0108	,,	,,
Dorsum of foot	0·0031	,,	,,

Both output per sweat gland and the number of glands in action are important. Thus the excitation of the sweating mechanism by mild muscular exercise is largely the result of an increase in the number of functional sweat glands with little or no increase in the output per gland More severe stimulation, such as partial immersion of the limb in hot water gives an increased output of sweat per gland in a given period of time as well as an increase in the number of functioning glands.

These results recall the earlier work of Randall (1946) who suggested that the first sweating response of a large skin area to heat is an increase in the number of active glands, each gland discharging a relatively smaller amount of excretion. As the heating continues, qualitative evidence of a secondary increase in sweating through greater output by the individual glands may be obtained. Randall also gives some information about variation in sweat gland activity While a subject is resting quietly in a warm environment the normal sweating responses consist of cyclical discharges by larger and smaller numbers of glands. During several successive cycles certain glands may be repetitively active while others are only occasionally active. In other words, considerable alternations are demonstrable among the glands of a given region during any one or any series of cycles. This interesting variation in functional activity recalls the corresponding phenomenon in the renal glomeruli made familiar to us by the classical work of Richards, and suggests that "an all or none" principle is applicable to the sweat glands.

Cohen (1950) too has measured palmar sweating by means of a blotter and a sensitive damped analytical balance. He finds that the values of palmar sweat for the right and left hands are highly correlated in individuals no significant difference could be established between the means in 54 individuals

Sweating rates do not necessarily agree on bilaterally symmetrical areas age differences are marked while little or no sweating occurs in the tip of the nose, elbow patella or dorsal surfaces of the metacarpal joints (Sulzberger and his colleagues, 1950 List and Peet 1938)

The factors which stimulate or depress sweating continue to excite much interest Some ingenious qualitative tests for the direct observation of sweating have been invented including the starch-iodine method of Randall (1946) the quinizarine powder method of Guttmann (1937) the tannic acid, ferric chloride method (Haimovici 1950) the silver nitrate method (Kadatz, 1950), direct observation of sweating under the plus 20 lens of the ophthalmoscope or the slit lamp (Jones, 1950 Kahn, 1951) measurement of electrical resistance (Whelan and Richter 1943) This list is not exhaustive. For quantitative study sweating may be increased by heating the patient through raising the external temperature (by electric blanket hot room hot bath or other means) or the metabolic rate by exercise, or by giving cholinergic drugs (15 milligrams of pilocarpine sulphate subcutaneously) The sweating rate is determined gravimetrically (Weiner 1945) due allowance being made for transepidermal loss of water (Felsher and Rothman, 1945)

It has been known for a long time that sweat glands receive nerve fibres from the sympathetic ganglia Dale and Feldberg (1934) first showed that these fibres are cholinergic in the cat and assumed that in man the sympathetic fibres supplying sweat glands are strictly cholinergic. They also pointed out that parasympathetic drugs promote or suppress the secretion of sweat in man Since then there has been much discussion about the nature of the innervation Coon and Rothmann (1941) demonstrated that sweating may be the result of an axon reflex, for acetylcholine, nicotine or α lobeline injected intracutaneously induce sweating on the pad of the cat's paw and in man which can be prevented by procaine infiltration. Randall (1947) showed that when the skin temperature of a circumscribed spot is raised above 40–41 C. by radiant heat local sweating commences which can be diminished but not completely stopped by procaine or atropine. Hence there are

three ways by which sweating can be initiated (a) by direct action on the sweat glands as with pilocarpine intracutaneously or by local heating, (b) through an axon reflex and (c) by means of reflexes through the higher levels of the central nervous system The temperature of the blood to the higher centres is important in this connexion. That cholinergic stimulation through production of acetylcholine is concerned in these processes is indicated by the experiments of Kahn and Rothman (1942) Janowitz and Grossman (1950) and Haimovici (1950) Janowitz and Grossman have shown, too that acetylcholine is constantly being produced from sweat gland nerves in subthreshold amounts and that anticholinesterases such as Prostigmin permit it to be built up above threshold levels. But several workers, including Sonnenschein, Kobrin and Grossman (1949) and Haimovici (1950) have produced evidence for adrenergic stimulation also Thus, dibenamine and ergotamine, adrenergic blocking agents, block spontaneous palmar sweating in man while an intradermal injection of epinephrine encouraged sweating in 84 per cent of human subjects investigated by Haimovici. Its sudomotor effect was inhibited by dibenamine in all cases. Ephedrine and arterenol also stimulate sweating. Such experiments suggest, therefore that the secretory activity of sweat glands is augmented both by cholinergic and adrenergic stimulation. Nor-adrenaline has recently been shown to possess sudomotor activity Obviously the matter demands further investigation before definite conclusions can be reached.

Inhibition of sweating has received some attention in recent years. Faulty and reduced outpouring of fully formed sweat may result from (1) plugging by horny material as in prickly heat and tropical anhidrosis, or in ichthyosiform itching eruptions, dry forms of atopic dermatitis, (2) scar-like obliteration of the superficial portion of sweat ducts, rather than mere plugging of their orifices, for example, after certain cases of lichenoid atabrine dermatitis, (3) application of antiperspirants or fat solvents (O'Brien, 1947) and (4) electrophoresis or by external application of cationic wetting agents and positive electrolytes.

For further details the reader is referred to the original paper by Sulzberger and his colleagues (1950), whose classification this is, and to Kadatz (1950) and Shelley Horvath and Pillsbury (1950). Finally the careful paper by *Kahn (1951)* on the loss of sweating after section of a peripheral nerve and its recovery with nerve regeneration contains much valuable information for the general surgeon as well as the skin specialist and physiologist.

THE SEBACEOUS GLANDS

Sebaceous glands are multiple acinar holocrine glands for the most part appendages of the external root-sheath of the hair follicles. They open on to the epidermal surface with hairs but in certain places they are free, especially in the palpebrae, nipples, prepuce and occasionally in the glans penis and labia minora. In man they are most numerous in the scalp, forehead, face and chin where Benfenati and Brillanti (1939) estimate there may be 400–900 glands per square centimetre of skin. The rest of the skin carries fewer than 100 glands per square centimetre. They are said to be larger and more numerous in the midline of the body especially of the back, but they are absent from the palms and soles and the dorsum of the foot (Clara, 1929).

Each sebaceous gland is composed of a number of acini made up of large dying central cells and small peripheral cells, like flattened *epidermal squames, con* gregated around a lumen filled with sebum The lumina lead to a common excretory duct opening into the upper part of its hair follicle. Mitochondria and Golgi bodies are found within the sebaceous cells but it is only the Golgi body that seems to be concerned in the production of sebum (Ludford 1925 Melczer and Deme, 1943 Montagna, Kenyon and Hamilton 1949 Suskind, 1951). Evidence given by Emanuel (1938) and Serrati (1938) suggests that sebum is formed at a good pace after removal from the skin by washing with ether approximately 50 per cent is replaced at the end of one hour and replacement is almost complete in about 4 hours. *The level reached is constant for a given area in any one* person and has been named the sebum level which is defined as the amount of sebum covering 1 square centimetre of skin

Slowing down of sebum secretion has been attributed to (a) inhibition of sebaceous gland activity by the pressure of the sebaceous layer (Emmanuel 1938), (b) a nervous reflex action (Serrati 1938) and (c) re-absorption of sebum as it is extracted from the glands (Doupe, and Sharp 1943) Some, too is dispersed along the sulci radiating from the sebaceous glands (Butcher and Parnell *1948*). Table I from Hodgson Jones and Wheatley (1952) gives an idea of the regional *variation in sebum production*

TABLE I

SOME SEBUM LEVELS OF VARIOUS SITES OF BODY OBTAINED BY GRAVIMETRIC METHOD OF ESTIMATION

Site of body	*No of subjects*	*No. of estimations*	*Sebum level (μg sq cm)*	
			Range	*Average*
Forehead	17	22	97 340	212±73
Chest	21	24	44–237	120±61
Back	27	40	21 268	106±56
Abdomen	13	41	25–227	67±45
Axilla	8	12	30–237	84±59
Arm	38	63	9–146	58±34
Groin	4	4	50–105	75±28
Leg	11	13	18– 82	36±19

The possibility of nervous control of sebaceous glandular activity is a much *debated question. It is true that* Boeke (1934) described a nerve plexus investing sebaceous glands and believed it to be sympathetic in origin and excitor in function although he noted that the individual glandular cells were not innervated Experi ments on animals afford some evidence in favour of nervous control but on the whole, there is little in favour of the view in the case of man (Goldsmith 1936 Doupe and Sharp 1943 Miescher and Schönberg, 1944 *Hodgson Jones*, MacKenna and Wheatley 1952)

The part played *by androgens in stimulating* sebaceous activity in man seems clear enough and castration leads to depression in sebum production. With oestrogens we again encounter uncertainty The reader is referred to the admirable short discussion by Hodgson-Jones, MacKenna and Wheatley (1952) for the

literature these investigators also give an account of some observations which associate cyclical activity of sebaceous glands with the menstrual pattern.

An interesting age relationship also exists. Sebum secretion is less in children than it is in adults, increasing at puberty and diminishing in old age. Before puberty the sebum level is approximately the same in all areas (Hodgson-Jones, MacKenna and Wheatley 1952).

Rises in temperature, local or general, increase the activity of the sebaceous glands but neither atmospheric pressure nor humidity has any effect (Butcher and Parnell, 1948).

Whether cellular regeneration and replacement goes on by mitotic division is a debatable question. Mitotic figures have been described both in the sebaceous duct lining cells and the glandular cells of experimental animals (Bullough, 1946 Parnell, 1949), but little is known about the human problem. The mechanics of sebum secretion, too would be a profitable study.

The composition of sebum has received careful attention in recent years from MacKenna, Wheatley and Wormall (1950, 1952). Table II, from Wheatley (1952) summarizes present knowledge.

TABLE II

CALCULATED AVERAGE COMPOSITION OF HUMAN* FOREARM SEBUM

Component	*Per cent*
Free fatty acids, unsaturated	15
saturated	15
Triglycerides	32·5
Waxes (including cholesterol esters)	15
Sterols cholesterol (free)	2·5
cholesterol (combined)	(2·5)*
other sterols	2·5
Squalene	5
Paraffins	7·5
Unidentified compounds (including *oxidized* squalene)	5

*Included in waxes.

The significance of most of these components is still unknown. Recently Burtenshaw (1942, 1948) has shown that self-disinfection of the skin is probably in part due to the free *fatty acids of sebum. Ricketts, Squire and Topley (1951) have* confirmed these findings and have shown that the sensitivity of certain micro-organisms to unsaturated fatty acids runs parallel to the rate of disappearance of these organisms from the skin. Rothman *and his colleagues (1947)* give evidence that certain saturated fatty acids play an important part in the spontaneous cure of ringworm. This fascinating field of investigation deserves further exploration by chemists, clinicians and histologists.

ANTIBODY PRODUCTION IN THE SKIN

For many years considerable interest has been shown in the production of antibodies and their site of origin has given rise to much conjecture. The relevant literature on this topic and closely allied problems is discussed in detail by Burnet

and Fenner (1949) while matters pertaining to cells and antibodies are to be found in the book by Cameron (1952) Until recently it was generally accepted that the reticulo-endothelial system is responsible for antibody formation, structures rich in this tissue, especially the spleen, liver and bone marrow being awarded priority in production. But the experiments of Ehrich and his co-workers (Ehrich and Harris, 1942 Harris and his colleagues, 1945) drew attention to the lymphocyte as a likely source of antibody for when antigens were injected into rabbits feet the efferent lymph from the popliteal gland was found to contain much more antibody than the afferent lymph and at the same time the lymphocytes in the efferent lymph had increased in number and there was reason to believe they had been recently produced in the associated gland But the theory was not altogether satisfactory and more recent work favoured the plasma cell as a possible source of antibody (Bjorneboe and Gormsen 1943 Bjorneboe and his colleagues, 1947 Fagreus, 1947 1948) Perhaps the difference of opinion is not very important, for the origin of these cells is still obscure and there is reason to think that they may all be closely related.

The introduction of an ingenious method for assaying antibody production in small pieces of tissue by Oakley and his colleagues (1949 1951 1953) has thrown new light on the subject They point out that the mere presence of high concentrations of antibody in tissue, as for instance, in the draining lymph gland of a rabbit s foot injected with an antigen, is not necessarily proof of local production of antibody for it ignores the likelihood of the leakage of circulating antibody into the inflamed lymph gland, and it involves the assumption that our methods of extraction are uniformly efficient, though it would seem evident that cellular organs like the spleen would more readily yield up their antibody than structures like skin or bone (Oakley 1953) However by injecting two antigens into two different sites, one in one region and one in another and determining the concentration of both types of antibody in the relevant tissue extracts these difficulties can be surmounted. If the antibody in the tissues leaks out of the circulation, then the ratio of the two antibodies will be the same as the ratio in the serum divergences from this ratio will suggest local production or storage of antibody Various other sources of error which we need not consider here are overcome, too, by the method.

The results have been surprising, for they give evidence of the production of antibody in the skin, fat voluntary muscle and cornea, but not in liver spleen or bone marrow of rabbits. Oakley does not maintain that the antibodies are formed by skin cells, fat cells or muscle cells, but suggests with proper caution that they may come from connective-tissue cells or the cells of the granuloma that develops rapidly around the injected antigen The investigation is still in its early stage and the results cannot of course, be transferred from the experimental animal to man without some preliminary direct tests. But if the conclusions hold for human skin then a fruitful new field will have been opened up for it would appear desirable to establish how far all sorts of antigen can produce their own antibodies in the skin, whether all skin regions are equally skilled at antibody elaboration and, above all, in what manner does the phenomenon contribute to local immunity to skin infection. We shall want to know too if genetic factors are concerned, whether the antibody function varies from individual to individual, throughout life and between the sexes and finally the physiological factors which

modify the output of antibodies of varying nature. Lastly every effort should be made to decide whether this skin property is a reflexion of the organism's capacity to respond, as a whole, to immunization.

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own marrow concentrates, was reproduced in its entirety. Incidentally the same plasma from the patient in whom the first artificial or *in vitro* technique was demonstrated, induced the LEP in 46 consecutive marrow preparations taken from as many patients with various haematologic problems.

The artificial production of the L.E. phenomenon with cell-free L.E. plasma showed clearly that the cells in the LEP were not of a specific type, such as megakaryocyte or metamyelocyte, but were mostly ordinary leucocytes rendered phagocytic by a factor in the plasma. This demonstration relegated to a secondary role the rosettes of leucocytes and the L.E. cells of the LEP for they were merely indicators for the presence of the L.E. factor (LEF) in the plasma. As in the opsonic index, in which ordinary leucocytes are attracted to bacteria and engulf them due to the presence of opsonin, the cells seen in the LEP were performing at the call of the special factor in the L.E. plasma. Final proof came with the demonstration that the bone marrow cells from animals, such as the dog and rabbit, would manifest the LEP when mixed with L.E. plasma or serum.

The *in vitro* induction of the LEP opened new avenues of investigation in lupus erythematosus. It is the purpose of this chapter to summarize much of these laboratory data, and to correlate them with the newer and broader clinical concepts of L.E.

THE L.E. PHENOMENON INVESTIGATIONS

Prior to the discovery of the L.E. factor much work had already been done on the cytologic changes of the L.E. phenomenon. In his original paper Hargraves (1948) indicated that the L.E. cell was a mature neutrophilic polymorphonuclear leucocyte, containing a homogeneous, purple-staining mass. The material, contained within the L.E. cells, stained with specific nuclear stain (Feulgen's stain) as did "free nuclear material observed in any bone marrow". It was apparent to Hargraves that in L.E. bone marrow preparations the polymorphonuclear leucocytes first gathered in rosettes and then phagocytosed nuclear material. The L.E. cell was considered to be "the result of a lytic-phagocytic phenomenon".

Cytochemical studies on the inclusions in L.E. cells revealed the presence of depolymerized desoxyribose nucleic acid (DNA) with an "increased ratio between optical density of Feulgen-stained and methyl green-stained inclusions compared with the respective optical densities of normal cells" (Lee, Michael and Vural 1951). From this and from other work done in his laboratories Klemperer (1952) concluded that the inclusions of Hargraves L.E. cells were optically and chemically identical with the haematoxylin-stained bodies described by Gross (1932) in post-mortem tissue sections. The haematoxylin-stained bodies have been established by Klemperer and his colleagues (1950), as characteristic tissue lesions in 32 of 35 cases of acute lupus erythematosus. This linkage between the L.E. phenomenon and the tissue changes at autopsy suggested to Klemperer a possible pathogenesis based upon a disturbance of DNA metabolism.

It is of importance to the basic understanding of lupus erythematosus to know whether the haematoxylin-stained bodies and the inclusions of the L.E. cells, granting an identity between them, are actually a primary tissue alteration. In other words, are these visible microscopic changes the site or the source of the disease? If these alterations represent a primary tissue aberration, then a study

CHAPTER 5

BLOOD FACTOR IN LUPUS ERYTHEMATOSUS

JOHN R. HASERICK

INTRODUCTION

IN 1946 HARGRAVES made the discovery of the lupus erythematosus (L.E.) phenomenon The L.E. phenomenon (LEP) is seen in haematologic smears in two stages (1) rosettes of leucocytes around nucleoprotein and (2) the L.E. cell, a leucocyte which has engulfed a round mass of the nucleoprotein (Plate I). The LEP is seen in concentrated bone marrow or peripheral blood preparations from a patient with systemic lupus erythematosus. Recognition of this alteration is the basis for all of the reliable L.E. diagnostic tests of the present day and for the detection of the L.E. factor in the blood. Morton under the guidance of Hargraves, reported the discovery in a thesis (1947)

The L.E. phenomenon (LEP) was first demonstrated in heparinized concentrates prepared from the bone marrow cells of patients with systemic lupus erythematosus.* Not stressed in the first regular publication on the LEP (Hargraves, Richmond and Morton 1948) was the all important technique of heparinizing and concentrating the marrow cells according to the method of Schleicher and Sharp (1937) Consequently the LEP was not readily found by others who used the direct smear rather than the concentration method of examining bone marrow preparations. For a time, use of the procedure as a diagnostic measure was not universally accepted. On the other hand, in laboratories where the Schleicher-Sharp heparinization and concentration technique was routinely employed the finding of the LEP was readily corroborated (Haserick and Sundberg, 1948)

Later the LEP was demonstrated in the cell concentrates of L.E. peripheral blood (Sundberg and Lick, 1949) Since the phagocytic phenomenon was not found in the direct smears, this again demonstrated the necessity for concentration of the cells in order to produce LEP The importance of cell concentration suggested that the alteration might not be primarily associated with the cells.

In February 1949 cell free plasma was taken from a patient ill with classic acute disseminated lupus erythematosus and was added to the heparinized bone marrow cells of a normal person (Haserick and Bortz, 1949) After mixing and concentrating the plasma and bone marrow preparations, smears were made from the buffy coat † and stained with Wright's stain in the usual manner It was found that the entire L.E. phenomenon as described originally by Hargraves in the patient's

* Systemic lupus erythematosus is used in this chapter to indicate lupus erythematosus confirmed by the demonstration of the L.E. phenomenon. Almost all cases of acute disseminated lupus erythematosus and about one-half the cases of subacute disseminated lupus erythematosus therefore, are considered here as "systematic."

† When blood is centrifuged three layers are formed—an upper pool of serum, a *middle* buff-coloured layer of leucocytes, and below this, a pool of red cells. Buffy coat is an accepted term *for the central zone—Editor*

The possibility remains that the haematoxylin-stained bodies of Gross and Klemperer are not identical with the nucleoprotein of the L.E. phenomenon. Berman and his colleagues (1950) while noting the identity between the haematoxylin-stained bodies and depolymerized nucleic acid, did not find corroborative evidence in favour of the view that the L.E. inclusion masses were the result of "depolymerization" of desoxyribose nucleic acid. Using methyl green and pyronine mixtures applied to L.E. cells in marrow preparations, the characteristic affinity for pyronine seen with depolymerization was not found.

THE L.E. FACTOR

The *in vitro* induction of the L.E. phenomenon provided an end point for the titration of the L.E. factor and opened a wide field of investigation. The effect of dilution of L.E. plasma with the resultant alteration and final disappearance of the L.E. cells has already been mentioned. The L.E. factor was found to be heat labile. When L.E. plasma was heated to 55° C. and then added to human bone marrow mixtures, L.E. cells were not found. After heating to 65° C. the rosettes of leucocytes disappeared. Contrariwise freezing did not change the production of the LEP

L.E. plasma, kept at room temperatures for 6 months, still induced the L.E. phenomenon. The same plasma lost its inclusion-inducing ability after contamination with bacteria. It was found that an L.E. plasma sample could be stored in a refrigerator indefinitely without loss of the L.E. factor Thus, L.E. plasma samples could be sent long distances for testing, providing sterile precautions were taken to prevent bacterial contamination. Incidentally attempts were made to keep the plasma samples sterile by adding merthiolate, but the antiseptic inhibited the marrow cells and prevented the formation of the L.E. phenomenon. Powdered penicillin failed to prevent bacterial contamination of the plasma samples. At present the plasma samples are drawn aseptically and mailed in sterile containers to centres where bone marrow material is available. This technique is used mainly as a check on L.E. tests, based upon peripheral blood buffy concentrates, in which a control L.E. test must, of course, be lacking.

Large numbers of drugs have been added to L.E. plasma prior to mixing with marrow cells, in order to test their effect on the L.E. factor The L.E. factor was not inhibited by the addition of cortisone, hydrocortisone corticotrophin, testosterone, oestradiol, progesterone or several antibiotics. It was inhibited by *para*-aminobenzoic acid, but presumably from a direct attack upon the bone marrow cells, rather than upon the L.E. factor itself

The following study was undertaken (Haserick, Lewis and Bortz, 1950) in order to identify the fraction of the L.E. plasma responsible for inducing the L.E. phenomenon. After initial studies had revealed that both serum and plasma were capable of producing the phenomenon, plasma was used in order to simplify and standardize the procedure. Before fractionation, samples of lupus plasma were dialysed. This did not change their ability to induce the phenomenon. Each plasma sample was then fractionated by the Tiselius electrophoretic technique. The fractions were added to normal bone marrow preparations. Each mixture

of the disturbance of DNA metabolism in lupus erythematosus seems indicated, and investigations along this line might lead to its pathogenesis. This attractive hypothesis is disturbed however by the *in vitro* induction of the L.E. phenomenon, which indicates that the L.E. cell inclusions and thus their counterpart, the haematoxylin stained bodies are merely secondary reflections of the presence of a characteristic factor in the plasma.

The *in vitro* studies showed that the L.E. phenomenon varied according to the concentration of the L.E. factor in the plasma. The ability to induce the L.E. phenomenon at will by adding cell free L.E. plasma to bone marrow cells permitted a breakdown of the entire phenomenon. First, it was possible to create the phenomenon by making a simple mixture of L.E. plasma with concentrated human marrow cells, and to make smears at 30-second intervals. By this method the rosettes of leucocytes were seen to form in 5–7 minutes, whereas L.E. cells were not noted until 12–15 minutes. Secondly by making serial dilutions of L.E. plasma prior to mixing with the cells, the L.E. cells were the first to disappear with dilution. The rosettes of leucocytes around the nucleoprotein did not disappear until the L.E. plasma was diluted to 1 32. Consequently the L.E. cells appeared to be the end result of a phenomenon of phagocytosis which began with the rosette-like adherence of neutrophils to nucleoprotein and ended with nucleoprotein mass within the neutrophils.

Since no appreciable amount of nucleoprotein is to be found in cell-free serum or plasma, the nucleoprotein of the L.E. phenomenon had to be derived from the bone marrow or peripheral cell masses. By an ingenious experiment Moyer and Fisher (1950) provided additional proof that nucleoprotein is of secondary importance in the L.E. phenomenon A comparatively pure suspension of neutrophils was obtained from the buffy coat of blood from patients with acute infections. This was mixed with L.E. plasma and then added to nucleoprotein from various sources, such as neutrophils, bank blood buffy material, and a suspension rich in lymphocytes (99·9 per cent) obtained from the blood of a patient with chronic lymphocytic leukaemia. After these mixtures were incubated smears were prepared and stained in the usual manner The mixture containing lymphocytic nucleoprotein showed an abundance of L.E. cells whereas, the other preparations, despite the presence of neutrophils and L.E. factor failed to reveal many L.E. cells. Thus, three elements are necessary for the formation of the L.E. phenomenon (1) active neutrophils, (2) nucleoprotein of lymphocytic origin and (3) the plasma L.E. factor One should bear in mind that these elements are essential regardless of the source of neutrophils. The L.E. phenomenon can be created in bone marrow peripheral blood or even in skin windows (Rebuck and Berman, 1950) providing these three elements are present.

It is appropriate to return to the question of the haematoxylin-stained bodies of the tissue sections, and their relationship to the L.E. phenomenon From the *in vitro* studies it is apparent that the inclusion of the L.E. cell is of secondary rather than of primary importance. In view of the apparent chemical and optical identity between the inclusion of the L.E. cell and the haematoxylin-stained bodies seen in post mortem sections, it is evident that the haematoxylin-stained bodies also may well be merely indicators for the presence of the L.E. plasma factor From these data at least, the L.E. factor rather than the haematoxylin-stained bodies would appear to deserve first investigation.

investigators induced the L.E. phenomenon in the peripheral blood of the animals. Only the female guinea pig proved susceptible. The animals developed fever loss of weight and leucopenia. Tissue changes were noted in the arterioles of the kidneys and lungs. Similar investigations have been reported in the excellent monograph by Marmont (1951).

THE L.E. TESTS

Methods

The L.E. tests of the present day are accurate diagnostic procedures for the detection of typical or atypical systemic lupus erythematosus. The degree of accuracy varies considerably however depending as much upon the familiarity of the laboratory with the criteria of a positive test as upon differences in technique. All L.E. tests are based upon either the *in vivo* or the *in vitro* production of the L.E. phenomenon.

Beerman (1951), Table I summarized the various techniques used to demonstrate the L.E. phenomenon.

TABLE I

SUMMARY OF OCCURRENCE OR PRODUCTION OF L.E. CELLS

In vivo	Heparinized bone marrow of L.E. patient	Hargraves *et al.*, 1948 Haserick and Sundberg, 1948
	L.E. peripheral blood, venous (heparinized blood) (oxalated blood) (centrifuged)	Sundberg and Lick, 1949 Hargraves *et al.*, 1949
	(in clotted blood of L.E. patients)	Gonyea *et al.* 1950
Produced *in vitro*	Human bone marrow and L.E. plasma	Haserick and Bortz, Mar. 25 1949 Hargraves, Apr. 27 1949
	Animal bone marrow and L.E. plasma	Berman *et al.*, 1950 Sundberg (dog), 1950
	Cellular elements of normal white cells plus L.E. plasma	Hamburger 1950 Moffat, Barnes, Weiss, 1950 Fisher and Moyer 1950
	As above, no anticoagulant	Barnes, Moffat, Weiss, 1950
In skin	Inoculation of normal skin with L.E. plasma	Rebuck and Berman, 1950
	Cantharides blister in patient with acute L.E.	Watson *et al.* 1951

To these procedures can be added other variations for detection of the L.E. phenomenon (Lee, 1951; Zimmer and Hargraves, 1952). A "pre-L.E." cell has been described by Sachs, Feldman and Morrison (1952).

was studied for rosettes of leucocytes and L.E. cells to determine which fraction of the L.E. plasma carried the responsible factor

Only the *gamma* globulin fraction produced the two stages of the L.E. phenomenon. The albumin fraction, and the combined albumin *alpha* and *beta* globulin fraction, failed to induce the phenomenon.

Subsequent investigations were concerned with a more complete identification of the L.E. factor within the *gamma* globulin fraction First, L.E. *gamma* globulin has been separated with the ultra-centrifuge without succeeding in layering out the L.E. factor Other physicochemical techniques also failed to separate the L.E. factor from the *gamma* globulin fraction

Treffers, Moore and Heidelberger (1942) found a difference in antigenic behaviour between the normal *gamma* globulin and a *gamma* globulin containing antibody" They reported that two serum proteins with the same electrophoretic mobility were distinguishable from each other by immunologic methods. This principle was supported by an investigation (Haserick and Lewis, 1950) designed to demonstrate a possible immunologic difference between L.E. *gamma* globulin and normal *gamma* globulin considering the difference to be the L.E. factor

The *gamma* globulin fractionated by the Tiselius electrophoretic technique from the plasma of patients with systemic lupus erythematosus was used as an antigen to induce antibodies in rabbits. Similarly antibodies were induced in control rabbits with normal human serum and with normal human *gamma* globulin. The antisera developed in these three groups of rabbits were added to the L.E. *gamma* globulin solution and, after precipitation, the supernatant fluid was added to bone marrow preparations. The L.E. phenomenon was not demonstrable after the L.E. *gamma* globulin was precipitated by anti L.E. *gamma* globulin rabbit serum. However after precipitation of the L.E. *gamma* globulin by anti-normal human serum, rabbit serum, or by anti-normal human *gamma* globulin rabbit serum, the L.E. phenomenon was induced by the supernatant fluid, indicating that the L.E. factor still remained unprecipitated. These studies suggest that L.E. factor is an immunologically distinct component of L.E. *gamma* globulin.

More recently attempts have been made to identify the L.E. factor at the tissue level by the preparation of post mortem organ extracts The intent of this approach is to locate the origin of the L.E. factor or at least the site of its greatest concentration Such information might be invaluable in understanding the pathogenesis of lupus erythematosus. Previous studies have located the L.E. factor not only in the plasma, but in pleural (Van Doormaal and Shreuder 1950) and pericardial fluid. Berman and his colleagues (1950) pointed out that serum taken from a patient 4½ hours after death induced the L.E. phenomenon

Extracts were prepared from the tissues of 4 patients who died at the Cleveland Clinic with systemic lupus erythematosus. The solutions were added to human bone marrow preparations in the usual manner While traces of the L.E. phenomenon were noted in several different organ extracts, only the thyroid extract from one patient induced the L.E. phenomenon in a clear-cut manner (two plus positive L.E. tests) Two of the patients died of renal complications at the time of their death, the L.E. tests became negative.

Of great interest is the recent work with the L.E. factor by Castillo Fernandez and Remedios (1952) By injecting L.E. blood into female guinea pigs these

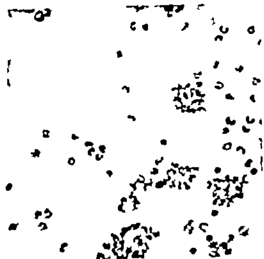


Fig. 1.—Dog marrow after addition of L. E. plasma, showing predominance of rosettes.

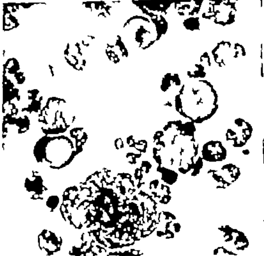


Fig. 2.—Human marrow after addition of L. E. plasma, showing one rosette and three L. E. cells. Large mass of nucleo-protein is seen in normal marrow.

L. E. PHENOMENON

PLATE I

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The plasma L.E. test

The routine L.E. test employed during the past 4 years at the special haematology laboratory of the Cleveland Clinic is the plasma-dog marrow preparation. Technique of the plasma-dog marrow L.E. test is given below

Obtaining dog marrow.—A heparin solution is prepared by diluting a 10-millilitre vial of Liquaemin Sodium, containing 10 milligrams per millilitre, in a litre of distilled water This stock solution is used for two purposes (1) to rinse the aspirating syringe before and during the repeated bone marrow aspirations, and (2) 2–3 drops of this solution are added to the paraffin tube immediately before placing the dog marrow in this tube.

The dog is placed on the usual "V" research table with the extremities tied down and a rope muzzle applied. The usual short bone marrow needle is introduced into the sternum between the ribs. A syringe which has been rinsed with the heparin solution is used, and the marrow slowly aspirated Tiny globules of yellow fat will be present if marrow is being aspirated. After the removal of 1–2 millilitres of marrow the needle may be placed one interspace away and the procedure repeated. As much as 8 millilitres may be obtained from each dog's marrow The same dog may be used as a marrow donor after 4 weeks. The large lean dog is preferable. After the syringe is emptied of bone marrow it is rinsed in distilled water and then in the heparin solution before it is used again Experience is needed to determine the proper amount of heparin solution to use. Too much will produce disintegration of the cells and too little will not prevent clotting.

Adding L.E. plasma.—One-half millilitre of suspected L.E. plasma is mixed with 1 millilitre of the prepared marrow solution. The mixture is allowed to stand 5–10 minutes, with occasional gentle mixing, and is then placed in a hematocrit tube and centrifuged at 1,000 r p.m for 5 minutes. The buffy coat is removed and stained with Wright's stain In a positive "plasma-dog L.E. test" rosette formation is particularly striking. *L.E. cells are seen only when the titre of the L.E. factor is high.* On the other hand, using human marrow L.E. cells are seen along with rosettes even in the "weak positive" tests. The rosette formation is as significant as the L.E. cells, both being an integral part of the L.E. phenomenon *Simple clumping of leucocytes without rosettes has no particular significance with respect to the diagnosis of lupus erythematosus.*

The reasons for the preferred use of this plasma-dog marrow technique are as follows

Ease of technique.—Since the aspiration of the dog marrow is carried out by assistants of the Research Division, the technicians of the haematology laboratory are spared the time and trouble of marrow preparation. For them, this procedure is easier than the methods using the peripheral blood.

Mass production.—Plasma samples are drawn at any convenient time and are refrigerated for testing later Using this procedure one technician can perform 20 plasma-dog marrow L.E. tests in less than 2 hours (Compare "Two-hour Blood-clot" method (Zimmer and Hargraves, 1952).)

Ease of reading.—A marrow preparation with its abundance of nucleoprotein and cells gives a well-defined, easily read smear which can be read in 20–30 seconds Peripheral blood L.E. tests, because of the sparsity of cells and nucleoprotein, often require 5 or more minutes of reading for satisfactory accuracy

Controls.—Only with plasma *in vitro* techniques are control preparations available for comparison. Dog or human marrow controls are made with both normal

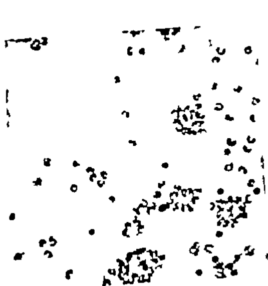


Fig. 1.—Dog marrow after addition of L. E. plasma, showing predominance of rosettes.



Fig. 2.—Human marrow after addition of L. E. plasma, showing one rosette and three L. E. cells. Large mass of nucleo-protein is seen in normal marrows.

[T face p. 8.

L. E. PHENOMENON

PLATE I

and known positive L.E. plasma. Control preparations are of particular value in the "weak positive" L.E. tests which are often of extreme importance in atypical cases.

Long distance testing.—Use of plasma permits testing in a central laboratory. Samples received in Cleveland from Hawaii have induced the L.E. phenomenon in dog marrow preparations. Precautions must be taken to prevent bacterial contamination.

Repetition of tests.—Since a 5-millilitre collection of plasma permits 8–10 plasma *in vitro* tests, the patient need not be disturbed for re-testing. When dog marrow preparations are doubtful, human marrow is used. This is obtained as extra material from routine bone marrow aspirations. Only the marrow of lymphatic leukaemia is unsatisfactory presumably because of the relative lack of neutrophils. If the results are still equivocal, a clotted blood technique is included.

Disadvantage of plasma L.E. tests

The main disadvantage of the plasma *in vitro* technique or any procedure using bone marrow is that it cannot be carried out easily in an office. This disadvantage may be outweighed by the fact that greater experience is needed in the interpretation of the L.E. phenomenon in peripheral blood preparations, due to the relative acellularity.

Another disadvantage may be a slight decrease in sensitivity of the plasma *in vitro* procedure as compared to any method not using heparin. Zimmer and Hargraves (1952), using procedures without anticoagulants as reported by Gonyea, Kalben and Marlow (1950) and Barnes, Moffat and Weiss (1950), found that the peripheral blood method was occasionally positive when other techniques, using heparin, were negative. Our experience with the peripheral blood technique is that it may be a little too sensitive. It may be positive when there is very questionable evidence of lupus erythematosus. Further experience over a several-year period is needed in order to evaluate the significance of weak positive L.E. tests seen in otherwise normal people.

Clinical application of L.E. tests

TABLE II

GRADING AND INTERPRETATION

Grade	*Dog marrow*		*Human marrow*	
	Rosettes per high-power field	L.E. cells	Rosettes per high-power field	L.E. cells
	3 or more	+	3 or more	+
	3 or more	0	3 or more	+
	1–2	0	1 2	+
	0–1	0	0–1	+
	Clumps of white blood cells, but no rosettes	0	Clumps of white blood cells, but no rosettes	0

TABLE III

SIGNIFICANCE OF GRADING OF PLASMA L.E. TESTS

Grade	*Significance*	*False positive*
+ + + + to + + +	1 Untreated systemic lupus erythematosus, severe 2 L.E. in relapse 3 L.E. responding poorly to treatment	0
+ +	1 Untreated systemic L.E., moderately severe 2 L.E. responding to treatment 3 Severe L.E. in uraemia	Penicillin and apresoline re-actions (rare)
+	1 2 and 3 above 4 Remission, spontaneous or steroid induced 5 Preclinical L.E.	
?	Significance unknown	

Walsh and Zimmerman (1953).
Unpublished data.

Value in atypical cases

The detection of the L.E. factor by means of the various *in vivo* and *in vitro* procedures is usually done without difficulty in patients with classic examples of systemic lupus erythematosus. However the L.E. tests may also be positive in less fulminating cases, many of which are unrecognizable as lupus erythematosus. It is in this group that the L.E. tests may have their greatest value. The acutely ill patient is now managed according to the present-day concepts of steroid therapy often with dramatic results. On the other hand, the patient with atypical lupus erythematosus may mislead the physician into a false sense of security. These patients may not appear ill. They retain, however the crucial characteristic of lupus erythematosus, namely the tendency to over react systemically to any inciting stress, whether it be a simple infection or undue exposure to ultra violet rays. The following example is presented in brief to illustrate this point.

Case A G., a male, aged 57 years, visited the Cleveland Clinic in July 1950, because of low grade rheumatoid arthritis. He was not acutely ill. The routine laboratory survey revealed a negative Wassermann reaction and a 1 plus positive Kahn test for syphilis. Because of the combination of rheumatoid arthritis and positive serologic tests for syphilis (Haserick and Long, 1952), an L.E. test was ordered and found to be weakly positive. The patient maintained his good health for 10 months. Then, following an upper respiratory infection, he became acutely ill with a severe illness manifested by anaemia, leucopenia, pleural and pericardial effusion. A diagnosis of systemic lupus erythematosus was made on the bases of these findings by a physician who was unaware of the history of a weak positive L.E. test.

False positive L.E. tests

False positive reactions are to be expected with any laboratory procedure, and L.E. tests are no exception of this rule. Experience has shown however that the L.E. tests are remarkably accurate in the detection of lupus erythematosus. Despite early reports of false positive reactions in a large number of different

diseases (Berman and his colleagues, 1950), a strong positive L.E. test usually means active lupus erythematosus. It is the weaker positive L.E. tests that occur in the fringes between false positivity and atypical lupus erythematosus. One and two plus L.E. tests have been seen in cases of apresoline toxicity (unpublished data) and in occasional penicillin reactions (Walsh and Zimmerman, 1953). In several thousand plasma L.E. tests (unpublished data) a + + + and + + + + grade has only been associated with systemic lupus erythematosus.

Indications for L.E. tests

L.E. tests are useful in establishing the diagnosis of lupus erythematosus, despite outward clinical appearances. Experience has shown that doubt may be cast upon the diagnosis of systemic lupus erythematosus when the L.E. test is negative. This is especially true when the patient appears to have classic acute disseminated lupus erythematosus, but does not manifest a positive L.E. test. Cases have been seen which were diagnosed by recognized dermatological and medical authorities as classic examples of acute disseminated lupus erythematosus, but the L.E. tests were negative eventually these cases were proved to be examples of trichiniasis, dermatomyositis, fever of undetermined origin and of short duration, and exudative erythema multiforme.

On the other hand, negative L.E. tests should not dissuade the clinician from the diagnosis of L.E. Repeated tests are indicated when in doubt. These should be done during periods of fever or obvious illness.

The following summary gives those cases in which the plasma L.E. test is indicated to aid the detection of lupus erythematosus in its atypical, subclinical stages (1) Rheumatoid arthritis (2) Positive serologic tests for syphilis (3) Epilepsy (4) Nephritis, polynephritis (5) Persistent leucopenia (6) Pleural or pericardial effusion (7) Purpura (8) Haemolytic anaemia (9) Repeated attacks of pneumonitis (10) Photosensitivity

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CHAPTER 6

CYTO-DIAGNOSIS IN DERMATOLOGY

A. TZANCK AND G. R. MELKI

IN DERMATOLOGY the first information about a lesion is furnished by its appearance. We know however to what extent the macroscopic appearance of lesions can be deceptive, and how fruitful those histological findings have been which have allowed us to distinguish between so many different structures, of which clinical examination did not provide even a hint.

The dermatologist, trained in anatomical-pathological methods, when he examines his patient, mentally superimposes on the morphological aspect of the lesions their histological structure, making the implied histo-pathological disturbances agree with the macroscopic lesion. Further improvements in histological technique have enabled us to analyse syndromes which were previously confused, and to make progress in the classification of certain dermatoses.

HISTOLOGY AND CYTOLOGY

Nevertheless, histology does not always provide the clinician with a definite answer The results which it furnishes are never immediate. Again, biopsy is not always possible, and to repeat it remains difficult if not impossible. Further histo-chemical studies always present difficulties when made on tissues modified by fixation, in spite of the remarkable progress achieved in this field.

That is why so many people have sought in cytology the remedy for these uncertainties. As it turned out, however cytological studies aimed at obtaining a rapid diagnosis were set on one side in view of the indubitable advances in histology

The fact that, since 1927 we have once more attacked this problem, is due to the appearance of numerous advantages which encouraged us in this effort.

The ease with which a specimen can be obtained, the acceptability of the procedure to the patient, who allows it to be repeated as often as may be necessary the possibility of working with "living cellular material" (the constituents of which are not altered by the processes of fixation) the rapidly obtained result, thus solving the problem of the time factor often so important in medicine all these are arguments in favour of the method of cytology

This method consists in the examination on a slide of scrapings, immediately stained, which are taken from dermatological lesions, just as in the examination of samples of blood. (Tzanck, 1947 Tzanck and Bourgeois Gavardin, 1947 Tzanck, Bourgeois Gavardin and Aron, 1948 Tzanck and Aron-Brunetiere, 1949).

This mode of investigation, in contrast with biopsy gives no information about the architecture of the tissues. Although no one would ever wish to substitute

it for histology the value of which is fully maintained, cyto-diagnosis furnishes very valuable information

Brocq introduced Methodical Scarification" as an aid to diagnosis (*see* Clemont Simon 1908) The curette may now be used to explore, systematically and minutely the different layers of the cutaneous integument, thus performing a kind of biopsy at one depth after another of the skin. *Surgical biopsy is* completed under the microscope, but methodical scarification remains a macroscopical manœuvre cyto-diagnosis bridges this gulf

TECHNIQUE OF CYTO-DIAGNOSIS

Cyto-diagnosis is to Brocq s scarification what *histo-pathological examination is* to the surgical removal of a specimen and because it represents a simple and rapid method, it provides an immediate laboratory extension of the clinical examination

Taking the specimen

The object to be attained is, therefore, the examination on a slide of a specimen from the lesion, produced by scraping or possibly by puncture.

The method of obtaining a specimen differs greatly according to the lesion. It must aim at obtaining the pathological elements themselves, and not crusts, scales, blood or products of cutaneous excretion, which may cover or mask them.

If one is examining a bulla, one removes the upper surface and carefully drains out the liquid. The specimen must be taken from the floor of the bulla.

If the lesion is infected, it must be cleansed of pus as thoroughly as possible.

If a neoplasm is being examined, it is necessary to remove the crusts and the hyperkeratic outgrowth the scarification must take place in depth, preferably at the edges of the tumour

In every case one must avoid drawing blood by vigorous tension of the skin around the lesion

The most convenient instrument for taking the specimen is Widal's scarificator Failing this, an ordinary vaccination stilette will do In any case, care must be taken not to remove too thick a scraping.

When the lesion under exploration is covered by an intact epidermis, scarification is set aside in favour of puncture *aspiration, performed with a needle* 0 7–0 8 millimetre in diameter It is thus possible to reach the lesion in depth without any troublesome haemorrhage.

Finally we have always found it useful, when biopsy has been necessary to take an impression on a slide of the excised fragment The cytological examination of these impressions *usually has enabled us to make a rapid diagnosis*, or at least to find some guide in making one, the later histo-pathological examination providing a useful check.

Staining

Up to the present, we have made systematic use of the *classical method of* staining, as worked out by Pappenheim and after him by May and Grunwald and by Giemsa.

TECHNIQUE OF CYTO-DIAGNOSIS

A small technical modification may save time in certain urgent cases (Tzanck, Aron and Rotenerweig, 1947).

As in the classical method, we begin by fixing with May-Grunwald solution containing methylene blue and eosin (about 20 drops on the slide) for 3 minutes. Then an equal quantity of distilled water at a strictly neutral pH, is added. After 2 minutes the stain is poured off and the specimen is covered with about 20 drops of pure Giemsa stain. Two minutes later the same quantity of distilled water is added and after 3 minutes the slide is washed.

Thus the whole time required for staining is reduced to 10 minutes, and all the stages of cytological diagnosis, from the removal of the specimen to its examination can be carried out, in case of need, in less than 20 minutes.

Interpretation of the specimen

The oil-immersion lens is used for examination, but it is useful, if not indispensable, to make a preliminary microscopical survey of the slide under a low magnification. It is, indeed, in this way that, with a little training, one learns to distinguish easily those pathological features the exact nature of which will be ascertained under high-power magnification.

It requires a certain amount of practice to interpret the slides. An observer used to haematological examinations will not find in these specimens any of the appearances to which he is accustomed. It must not be forgotten that it is from the products of tissue debris that the diagnosis has to be made.

One soon learns, however, to distinguish pathological elements from those to be observed in a normal condition. In this connexion it is first essential to realize that a normal epithelium parts from its cells with difficulty. Even energetic scratching only removes a few isolated cellular elements, or a few sparse clusters of cells with small dense nuclei, and clear basophilic cytoplasm irregularly distributed around these nuclei.

The appearances found in some specialized pathological states are extremely different (Tzanck, Aron-Brunetiere and Melki, 1950; Melki and Aron, 1950; Moline, Aron and Martin, 1947).

Although we have had more than 25 years experience, it is still impossible for us to draw up a full report covering all the results obtainable from cyto-diagnosis. But we can describe a certain number of conditions in which this method of investigation is of great use and rich in information. They include the following lesions (1) *Tumours* (*a*) naevo-carcinomas (*b*) cutaneous epitheliomas, (*i*) basal-cell, (*ii*) prickle-cell, (*iii*) intermediate (*c*) dyskeratoses (*d*) sarcomas. (2) *Bullous dermatoses* (*a*) pemphigus (*b*) Duhring Brocq's disease (dermatitis herpetiformis) (*c*) (*i*) herpes zoster (*ii*) herpes simplex and (*iii*) chicken-pox (varicella).

CYTO-DIAGNOSIS OF TUMOURS

Naevo-carcinoma (melanotic carcinoma)

Cyto-diagnosis in doubtful cases

An account of 2 clinical cases will explain, better than any general description, the capital importance of cyto-diagnosis in naevo-carcinoma.

Case I.—Initially the patient appeared to be suffering from a typical botryomycosis hominis (granuloma pyogenicum). This disorder is essentially benign, but, as has been



FIG 11 —Naevo-carcinoma very large cell with 2 giant nucleoli.

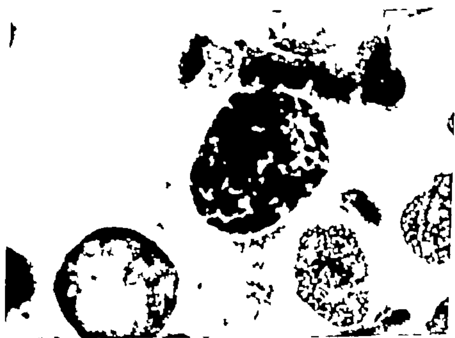


FIG 12.—Naevo-carcinoma pigment in a naevo-carcinoma cell.

shown by Ferrand and Dobkevitch, a naevo-carcinoma may present the same clinical picture. We carried out cyto-diagnosis, which revealed the presence of the cells typical of naevo-carcinoma, as described below. Now the method of treatment is utterly different for these two disorders. Adequate curettage, which should suffice for the treatment of pyogenic granuloma, would but aggravate the course of naevo-carcinoma—a tumour which requires extensive destruction by electro-coagulation.

Case II.—A still better demonstration is provided by the second case, in which the patient was admitted, in March 1946, to the Henri IV ward of the Saint Louis hospital, to await the result of a biopsy performed on a small nodule in the thigh. A fortnight after the biopsy a crop of very hard, rounded, painless, intradermal nodules which had the colour of normal skin appeared all over the body.

As in the previous case clinical examination did not suffice to provide an exact diagnosis. The biopsy was carried out by Dr Civatte, who promised us a reply within 8 days. In the interim, we ourselves punctured one of these swellings. The specimen contained sarcomatous cells and pigmentary elements, pointing to a diagnosis of naevo-carcinoma: this was confirmed by the biopsy. It is legitimate to ask whether an early diagnosis, permitting immediate electro-coagulation, would not have averted the wide-spread dissemination of the malady.

The cells of naevo-carcinoma

The cells seen in naevo-carcinoma have the appearance of large spherical or ovoid bodies, the cellular envelope of which is always intact.

The nuclei are always enormous: they are often rounded, but sometimes are irregular in shape with nodular excrescences. The chromatin network contains larger or smaller masses or granules. It is often divided into clearly defined streaks or whorls. There are always 2 or 3 nucleoli, which sometimes reach enormous dimensions (Fig. 11). Not infrequently mitoses are encountered, but these are less common than in prickle-cell epithelioma. There is a variable quantity of intensely basophilic protoplasm which often is finely granular. The pigment is variable in its distribution and is scattered unevenly through the cytoplasm: while it cannot be found in the so-called white naevo-carcinoma (derived from naevus anaemicus) it abounds in other cases, being present in the cytoplasm in the form of minute granules or of enormous masses, which smother the nucleus (Fig. 12).

Side by side with these giant melanoblasts, there may be cells with very small nuclei and very abundant cytoplasm, crammed with granules of pigment. These cells are reticular macrophages, which have phagocytosed the pigment liberated by the cells of the naevus. It is important to recognize these, in order to avoid the diagnostic mistake of failing to differentiate naevo-carcinomas from baso-pigmentary epitheliomas.

Cutaneous epitheliomas

Basal-cell epithelioma

Such a mistake ought not to be made, so different is the appearance of a basal-cell epithelioma from that of the tumour described above. Basal-cell epithelioma (Fig. 13) is revealed in the specimen by a great abundance of cell-clusters, the general arrangement of which recalls a bunch of grapes.

Inside these bunches, the cells have a remarkably monomorphous appearance. The nuclei, highly coloured, fairly large, oval, and of uniform dimensions, occupy

almost the whole of the cells. Nucleoli are rarely seen The protoplasm forms a narrow zone, *very slightly coloured* without any tendency to keratinization.

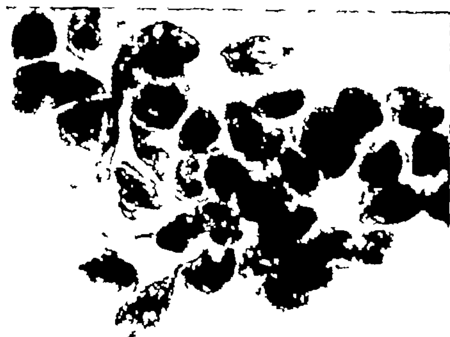


FIG 13 —Basal-cell epithelioma



FIG 14 —Prickle-cell epithelioma.

Prickle-cell (squamous-cell) epithelioma

Whilst the cells of basal-cell epithelioma are *monomorphic* in appearance, those of prickle-cell epitheliomas are polymorphic (Fig 14) and whether they are isolated or in clusters, are irregular in size, and often are very large.

The nucleus is clear irregular sometimes with nodular excrescences, and often pyknotic. Nucleoli are often very noticeable, frequently of abnormal proportions, but without reaching the giant size of those of naevo-carcinoma.

The cytoplasm is very abundant and often keratinized. In the latter case, it stains cobalt blue. In other instances the cytoplasm is less abundant, granular in appearance and intensely basophilic the nucleus is then bloated and enormous, giving the cell an amoeboid appearance.

Intermediate (transitional) epithelioma

Between these two extreme types we find, in certain scrapings, clusters of cells which have fairly abundant cytoplasm, and fairly large nuclei with well-marked

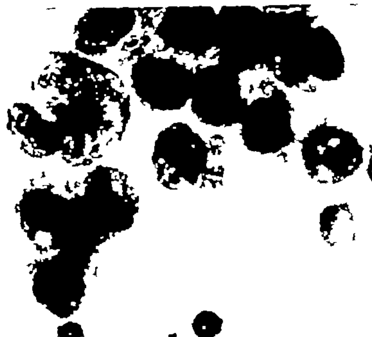


FIG. 15.—Intermediate (transitional) epithelioma.

nucleoli (Fig. 15) but in which there are not the nuclear monstrosities, the large amount of cytoplasm, nor the keratinization of prickle-cell epithelioma. It may be said of these cells that they are not basal cells, nor on the other hand, are they prickle cells. What we do see here are probably the ill-defined forms isolated by Darier and Ferrand, and called by them intermediate epithelioma (transitional epithelioma).

The tumours are difficult to distinguish clinically from basal-cell epitheliomas, but their course tends to be like that of prickle-cell epitheliomas. These neoplasms always present a histological problem, to the solution of which cyto-diagnosis may in time, make some contribution.

Cyto-diagnosis of the dyskeratoses

Here, once more, the importance of cyto-diagnosis certainly lies in the possibility of a proof of dyskeratosis still more, however it enables an easier and more profound study to be made of the detailed structure of the cells involved, than is possible by histological methods.

Molluscum contagiosum

Cyto-diagnosis has made it extremely easy to find the "round bodies" (*corps ronds*) ovoid corpuscles, larger than normal epithelial cells, deprived of their nuclei and seeming to be entirely keratinized, concerning which the term dyskeratinization is legitimately applicable. This finding confirms the clinical diagnosis.

Darier s disease (follicular dyskeratosis)

On cytological examination of a scraping, fairly large numbers of unusual epithelial cells are seen (Tzanck Aron and Melki 1950) rounded or oval in shape, they differ from normal horny cells by their rather smaller size. Occurring in isolation, these cells have a clearly defined periphery and do not present the geographical contour of the normal epithelial cells found in a scraping. Their nuclei are rounded and their peripheries are difficult to differentiate from the surrounding cytoplasm they are dense, and form a homogeneous block. No chromatic detail can be observed. The rather scanty cytoplasm forms an almost regular belt around the nuclei it is homogeneous and has a light brown (*bistré*) colour These cells correspond to the horny grains" (*grains cornés*) described in histological sections in Darier s disease. Darier by the way advised for diagnostic purposes the microscopical analysis of the crusts, and still more of the subjacent material after maceration in a solution of ammonia or formic acid, in order to isolate these characteristic forms.

In addition to the cells described above, there are others, the nuclei of which although showing the same characteristics on staining (absence of any definite chromatic structure) are larger in size. The cytoplasm immediately contiguous with the nuclei, is only slightly coloured, forming ill-defined areolae, which merge as they near the cellular peripheries into deeper staining, tawny yellow protoplasm, in which small granulations are scattered.

Another characteristic to be noted is the presence of cells which, although grouped in clusters, remain independent of one another and have clear-cut edges, indicating a certain degree of acantholysis. These cells have fairly large nuclei, with one or two small nucleoli The chromatin is present in a large number of small aggregations dark, very compact, scattered over a lighter base, which makes them seem to be surrounded by a paler frill The cytoplasm is abundant, regular in distribution, containing scattered small granulations, and staining a light brown (*bistré*) shade.

Bowen s disease and erythroplasia

These precancerous conditions may be grouped together for in all the cases of erythroplasia encountered by us, apart from certain details, we have found the same cytological picture. It may therefore be postulated that erythroplasia is often a clinical form of Bowen s disease affecting mucous or semi-mucous surfaces.

Examination of scrapings reveals a certain degree of polymorphism in the

arrangement, as well as some notable cytological peculiarities (Coste and Piguet, 1900 Civatte, Aron and Melki, 1950 Tranck and his colleagues, 1951 Sidi and Dobkevitch, 1947). The first point to be noted is the presence of cells which, although grouped in clusters, remain independent, and have well-defined borders indicating a certain amount of acantholysis. These cells usually have a large nucleus with one or two nucleoli. The chromatin is present in a large number of small aggregations, dark, very compact, scattered over a clear base. The cytoplasm is abundant and has a regular contour scattered through it are minute granulations staining a light brown (*bistré*) colour

Such cells generally vary greatly in form. In particular some nuclei are 4–5 times larger than others, and are irregularly shaped or even show excrescences.

This appearance corresponds to the poikilokaryonosis described in histological sections.

In the scrapings some epithelial cells of a very remarkable appearance are also found. Rounded or oval in shape, they differ from the cornified cells by their rather large size. Isolated from one another these cells have a well-marked cellular outline, but do not show the geographical contour of normal epithelial cells. The nucleus is rounded and its outlines are difficult to differentiate from the surrounding cytoplasm. It is dense, forming a homogeneous block. No chromatin detail can be observed. The rather scanty cytoplasm forms an almost regular zone. It is homogeneous, of a very dark brown tint. These cells correspond to the horny granules.

In addition to these cellular types, there are other cells, distinctly larger the nuclei of which while showing the same characteristics on staining (absence of definite chromatic structure) are smaller in size. The protoplasm is abundant and more spread out. The cytoplasmic zone, immediately contiguous with the nucleus and staining very lightly makes a kind of ill-designed aureole around it, which gives place towards the periphery to a protoplasm staining more darkly in a brownish-yellow tint, through which are scattered minute granulations.

Thus the positive cytological diagnosis depends upon three features (1) the presence of horny cells (2) poikilokaryonosis (3) the presence of segregated cells.

Finally another very special feature is, as a rule, the coloration of the cytoplasm of these segregated cells. With May-Grunwald and Giemsa staining, the cytoplasm of the horny cells is cobalt blue in colour that of the deeper layers seems to be more or less basophilic. In these isolated cells the cytoplasm stains a brownish-yellow in varying shades, light or dark.

The differential cytological diagnosis might be made, neither from basal-celled epithelioma, with its characteristic clusters, nor from prickle-celled epithelioma, but rather from epithelioma of the intermediate type. The irregularity of size of the nuclei might point to poikilokaryonosis but the absence of cornified granules, and of segregated cells, and the peculiar brownish-yellow colour of the cytoplasm permit the rejection of this diagnosis.

Paget's disease

Although the number of cases of Paget's disease which we have been able to study is not great, the cytological appearance of the scrapings has seemed to us to be very characteristic. The scrapings are rich in cellular elements, at first sight suggesting a malignant tumour Although often aggregated, the cells clearly

retain their cellular outlines, and remain independent of one another thus demonstrating the intensity of their segregation. Most of the cells are of enormous size. Their nuclei which are markedly basophilic, are irregular in size, sometimes appearing in duplicate or triplicate nucleoli are seen The chromatin is dense and is distributed in irregular masses The cytoplasm is abundant, is often vacuolated, and sometimes contains pigment granules.

Cyto-diagnosis of sarcoma

We have had an opportunity of examining a certain number of cases of sarcoma both cutaneous and ganglionic (Tzanck, Aron-Brunetiere and Melki, 1949). In all these, we were able to confirm the diagnosis by cytology However rather than reporting on each case, with a cytological description of the lesions, so monomorphous is the cellular appearance in every case that it seems more useful to us to endeavour to analyse the characteristics of the sarcomatous cell

The first feature which claims attention in the examination of scrapings from a sarcoma, whatever its type, is the monomorphism of its composition. When the lesion is ganglionic, this immediately enables a comparison to be drawn with the polymorphism of lympho-granulomatous tissue. Although differences in volume can be noted as well as of details in cellular morphology one does find in every cell, the characteristics summarized below

First, their size is very often increased and the ratio of nucleus to cytoplasm is always *higher than normal*

The cytoplasm is, as a rule, faintly coloured, only slightly basophilic and variable in morphology according to the type of sarcoma under examination, *but usually* vacuolated. One often finds cytoplasmic inclusions, difficult to identify

The nucleoli are numerous (4–6 in number sometimes more), and are always easily seen in the preparations because of their colour and of their clearly defined chromatic outline. They are pathological also in their shape and dimensions. Finally it must be emphasized that the ratio of nucleoli to nuclei is always high.

Mitotic figures are numerous and often abnormal, and amitosis (segmentation of the nucleus) is still more common

The nucleus is the essential and the most valuable element in the diagnosis of sarcoma, not only on account of its volume (which is often enormous—bloated, excrescent and irregular) but also because of the appearance of its chromatin this, which is very delicate and finely constructed takes the form of a fine network, regular but punctuated by slight thickenings at the points of intersection of its fibrils. A final point is that the nucleus often shows vacuolar degeneration, so that it appears to be systematically riddled with rounded holes.

In sarcoma, cyto-diagnosis has not only enabled us to confirm in every case the malignancy of the lesion and its sarcomatous nature, but has seemed to us to be *the most useful tool in the* work of determining the factors for the classification of these tumours.

CYTO-DIAGNOSIS OF BULLOUS DERMATOSES

Here, again cyto-diagnosis renders valuable service, particularly in the often *very difficult diagnosis of pemphigus.*

All the signs which form the basis of the differential diagnosis between

pemphigus and Duhring-Brocq's disease (dermatitis herpetiformis) may be absent pruritus, eosinophilia, sensitivity to potassium iodide, preservation of general well-being and the progress of the disease in wave-like exacerbations are not invariably noted in dermatitis herpetiformis. Nikolsky's sign is often absent in pemphigus.

The opposite is the case with the bullae, the structure of which differs profoundly in the two maladies. In Duhring Brocq's disease these lesions develop at a plane of cleavage, which is either epidermal (for deep-lying bullae) or corneous (for superficial bullae). In pemphigus, by contrast, the process is primarily cellular and evolves within the malpighian layer. The cells lose their connecting filaments and become segregated. This acantholysis gives rise to a cavity not in the plane of cleavage but right inside the epidermis: this cavity is filled with what Civatte (1947) calls "cellular mud" (*boue cellulaire*). Cyto-diagnosis enables this fact to be demonstrated with ease (see also Cordero 1947. Tzanck and Aron-Brunetiere, 1949b).

Cyto-diagnosis of pemphigus

In all the cases of pemphigus which we have observed, we have found an identical picture, so constant that we feel impelled to regard it as an absolutely positive sign in the diagnosis of this disorder (Tzanck, 1947b. Tzanck and Aron-Brunetiere, 1949a. Tzanck, Melki and Damoiseau, 1950).

What immediately arrests the attention in the examination of these scrapings are two simultaneous findings: (1) the extraordinary abundance of malpighian cells freed by the scarification and (2) the monomorphism of arrangement.

All the cells, even those which remain grouped in clusters, show a generally rounded form, corresponding to the disintegration of the malpighian layer. Careful examination reveals, indeed, that they either are or are becoming segregated (Fig. 16).

The nuclei are spherical and only slightly coloured, and nucleoli are present. The cytoplasm, which is abundant, basophilic, and relatively clear round the nucleus, becomes more dense at the periphery of the cell, forming a very distinct dark-blue areola.

The volume of these elements varies according to the type of pemphigus in question. Thus in pemphigus vulgaris, which is described above as *typical*, the cells are only slightly larger than normal and the nuclei *slightly hypertrophied*: all the cellular elements of the same scraping will be seen to be of similar size.

In subacute pemphigus, however, in addition to the cells described as occurring in pemphigus vulgaris, very large and apparently malignant cells may be found, having excrescent nuclei, tending to be divided, and with large basophilic nucleoli. These abnormalities are so great as to suggest, at first sight, the presence of a malignant tumour.

Finally, in Senar Usher disease (pemphigus erythematodes) the cells are less abundant, are very uniform, and hardly exceed the size of normal epithelial cells.

Duhring-Brocq's disease (dermatitis herpetiformis)

Nothing resembling these findings is to be seen in scrapings from the bullae of Duhring-Brocq's disease (Fig. 17) in which the sparseness of the material contrasts at the first glance with the richness of the specimens taken from pemphigus.



Fig. 16.—Pemphigus.

Fig. 17.—Duhring Brocq's disease (dermatitis herpetiformis).

In the bullae are found principally cells originating in the blood polymorphonuclear neutrophil, or sometimes a few eosinophil leucocytes (It is important to note that the eosinophilia, which is a haemic sign in Duhring's disease, is not a cytological sign) lymphocytes, monocytes, erythrocytes, and occasionally epithelial cells, which are as difficult to detach with the scarificator as it is easy by the same means to remove the "cellular mud" of pemphigus. These epithelial cells have the normal appearance described at the beginning of this section, and show no tendency to segregation.

As might be expected, scrapings from the bullae of erythema multiform, from an iodide or bromide eruption, from bullous eczema, and from artificially produced bullous dermatoses show the same picture as the scrapings in Duhring Brocq's disease. Further we have found in erythema multiform and in iodide and bromide eruptions, not only blood corpuscles and a few normal epithelial cells, but also a remarkable number of reticular macrophage cells. Is this finding a sign of special significance or only one related to the age of the bullae? That is a point which remains to be clarified, although we incline towards the second hypothesis.

In fact, the bullae of iodide and bromide eruptions, of erythema multiform and of Duhring-Brocq's disease all belong to the same *group of bullae* with a reactive significance (in contrast to the bullae of pemphigus, which are of dystrophic origin). There would therefore be no reason for any particularly notable difference between their cytological pictures.

Herpes simplex, herpes zoster and chicken-pox

Another group of bullous dermatoses has equally consistently confronted us with a typical cytological appearance. These are herpes simplex, herpes zoster and chicken-pox (varicella). In any of these disorders, cyto-diagnosis shows extremely polymorphic cells (Fig. 18), which vary from epithelial cells of normal size and shape and with an appearance of segregation, as found in pemphigus, to giant cells as large as megakaryocyte, with misshapen and often fragmented nuclei every kind of transitional form may be found.

In spite of the presence of small segregated cells, it is impossible to mistake these scrapings for those from pemphigus, in which the cellular elements are always more abundant, and in which one never finds this polymorphism nor any giant cells.

Between these two extreme types of cell, all transitions of shape and size may be found. It seems as though what we see corresponds to the various stages of that degeneration to which Unna (1900) gave the name of "balloon degeneration" but what we have observed has really nothing to do with ballooning, for what is happening is an enormous hypertrophy of the nucleus.

IMPORTANCE AND SCOPE OF CYTO-DIAGNOSIS

The importance of cyto-diagnosis should be sufficiently clear from the facts recorded above. While cyto-diagnosis permits a positive diagnosis of these various disorders, it also has its value *in excluding* others. One may be faced with one of the many cutaneous neoplasms which is difficult to identify cyto-diagnosis enables one rapidly to decide whether or not the lesion is malignant.



Fig. 18.—Herpes simplex, herpes zoster and chicken-pox: various cellular types.

The reliability of the method and the valuable services which it renders when biopsy cannot be performed or cannot be repeated, have established its worth. Nevertheless it would be a mistake to regard cyto-diagnosis as a rival to *histology* for *it is essentially complementary to that branch of investigation.*

Only by histological examination can lesions be studied in their entirety and only by histological techniques can we understand the significance of disturbances

in the architectural structure of the tissues. Often a diagnosis cannot be made by cytology but then histological techniques may be employed to achieve a diagnosis.

Nevertheless, although one cannot envisage cytology supplanting histology it retains its full value and provides very valuable information. It is, however riveted to clinical observation, and is dangerous without its clinical attachment. Reduced to these proportions, it is a remarkably good tool.

Cyto-diagnosis by phase-contrast microscopy

In proportion as the scope of cyto-diagnosis is closely defined, so its possibilities appear greater and greater. Since 1950, we have been studying scrapings under a phase-contrast microscope (Tzanck and Melki, 1951). The first result of this innovation seems to have been attained. It has been ascertained that immediately without staining, it is possible to diagnose the disorder by a simple inspection, under phase-contrast microscopy of the scrapings taken in basal-cell, intermediate or prickle-cell epithelioma, naevo-carcinoma, pemphigus and certain other disorders (Tzanck and Melki, 1952. Tzanck, Albahary and Melki, 1953).

We must point out that, in addition to the possibility of such an extemporaneous diagnosis of the lesion, examination by phase-contrast microscopy permits of a closer study of certain cytological details.

Cyto-chemical studies

Further cyto-diagnosis has always seemed to us to provide a possible means of study of cellular chemistry.

In this connexion, we have been able to study with Madame Steinbuck the content of sulphydril groups in cells obtained from various bullous disorders, including herpes zoster and pemphigus (Tzanck, Steinbuck and Melki, 1950). We have also been able to determine the influence of aureomycin on the sulphydril groups, and to work out a cyto-chemical method for the study of melanogenesis.

It seems, therefore, that cyto-diagnosis may be a method of widening the field of investigation.

ENVOI

Just as we cannot think of excluding any clinical methods—palpation, inspection and so forth—so we must not deprive ourselves of this new mode of investigation, which every day seems to us more and more worthy to take its place among the techniques of examination which the dermatologist has at his command.

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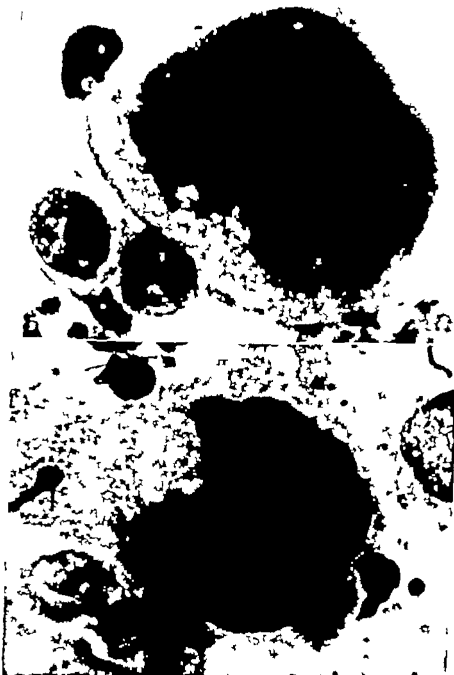


FIG 18 —Herpes simplex, herpes zoster and chicken-pox various cellular types.

The reliability of the method, and the valuable services which it renders when biopsy cannot be performed or cannot be repeated, have established its worth Nevertheless it would be a mistake to regard cyto-diagnosis as a *rival to histology for it is essentially complementary to that branch of investigation.*

Only by histological examination can lesions be studied in their entirety and only by histological techniques can we understand the significance of disturbances

CHAPTER 7

TUBERCULOUS DISEASES OF THE SKIN

G B Dowling and G Wetherley Mein

CLASSIFICATION

The classification of tuberculous diseases of the skin proposed by Darier in 1896 has undergone little alteration during the present century Darier divided the cutaneous manifestations of tuberculosis into two groups, those in which the tuberculous cause could be plainly established by the demonstration of tubercle bacilli in the lesions and by infecting experimental animals with the diseased tissue, and those which usually failed to satisfy such absolute criteria. On the other hand the second group satisfied other criteria so often that a direct relationship with tuberculosis might be supposed to exist particular importance was attached to histological structure and the co-existence of tuberculous disease elsewhere. The first group he named tuberculoses or true tuberculoses in the second group he included a number of well-defined and well-known dermatoses of eruptive type, under the name of tuberculides. A few dermatoses tentatively classed as tuber culides by Darier are now excluded, notably lupus erythematosus and granuloma annulare and one, the rosaceous tuberculide of Lewandowsky has been tentatively added to the list. In addition, erythema nodosum, though not included in the established list of tuberculides, is sometimes an early manifestation of tuberculosis, and Hohmann (1947) described under the name of initial erythematous tuber culide an erythema multiforme like eruption sometimes associated with erythema nodosum, which he observed in Holland during World War II in a number of cases of primary infection of the lung. As matters stand the full list is as follows

Tuberculoses or progressive tuberculosis of the skin

(1) The primary complex

(2) Tuberculous ulceration secondary to more or less advanced pulmonary tuberculosis and found most often in the mouth or about the mouth and the anus

(3) Tuberculous lupus, fungating tuberculosis of the skin and verrucous tuberculosis

(4) Tuberculous gumma, or colliquative tuberculosis.

Tuberculides

(1) Lichenoid tuberculides (lichen scrofulosorum and tuberculosis lichenoides (Ockuly and Montgomery 1950))

(2) Papulo-necrotic tuberculides, which include folliclis and the acneiform tuberculide (acne scrofulosorum)

(3) Miliary lupus of the face (T Ilbury Fox) acne agminata (Crocker) acnitis (Barthélemy)

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of the mouth with regional suppurative tuberculous lymphadenitis. A high proportion of the primary infections (10 out of 28 cases) was found on the lower extremities. Only one case presented with a systemic illness—a pyrexia followed measles and later the patient developed miliary tuberculosis.

A number of cases apparently of primary tuberculosis of the skin of the face and the elbows resulting from inoculation into abrasions mainly sustained in swimming pools have been reported from Sweden (Bruch, 1952 Hellerstrom 1952) The primary sore was always associated with regional adenitis without suppuration. A mycobacterium practically indistinguishable from Koch's bacillus was isolated from some of the cases, which, however differed clinically from classical primary tuberculosis of the skin in that there was no suppurative regional adenitis. The literature is summarized by Hellerstrom who states that the problem of tuberculous and similar infections acquired in swimming-pools is complex and remains to be solved

Little has been added for many years to our knowledge of the clinical features of the other forms of progressive tuberculosis of the skin. Of the tuberculides, lichen scrofulosorum appears to be rare in these days and some of the younger generation of dermatologists have perhaps never seen it. Ockuly and Montgomery (1950) distinguish what they call lichenoid tuberculosis from the better known lichen scrofulosorum The condition which they describe and illustrate consists of flat topped papules not of follicular distribution and usually occurring on the extremities. Each lesion is a little tubercle composed of endothelial cells and often with central caseating necrosis. The majority of cases are Mantoux negative. They regard the condition as a sub-group of the haematogenous forms of cutaneous tuberculosis.

Some doubt appears to exist concerning the comparative status of miliary lupus of the face of Tilbury Fox, acne agminata of Crocker and acnitis of Barthélemy In Great Britain a distinction is often made between the last named and the others, those cases in which the lesions or some of them become frankly pustular being termed acnitis while those which persist as solid discrete papules are given one of the other titles. The French apparently make no sharp distinction—Civatte in 1947 regarded lupus miliaris and acnitis as frankly identical. Degos (1953) states that when acnitis consists of solid papules as opposed to those examples which *exhibit* a tendency to break down, the condition approaches Tilbury Fox's miliary lupus of the face. In this group the histology is similar to that of the lichenoid tuberculide described by Ockuly and Montgomery (1950), and again some cases are Mantoux negative. It is hardly ever possible to discover any evidence of active tuberculosis elsewhere in the body in this condition or to make any noteworthy impression on its course with antituberculous chemotherapy and belief in its tuberculous origin is based on histology

The rosaceous tuberculide of Lewandowsky is usually not included in French classifications of tuberculosis. Nevertheless, the disease exists and it is well defined and recognized without great difficulty The question at issue is whether it is tuberculous or not.

The original report of Lewandowsky is quoted by Wile and Grauer (1935) as follows

The eruption on casual observation gives one the impression of rosacea not only because of its distribution over the forehead and cheeks (the nose being involved

(4) Hypodermic tuberculides indurative erythema of the lower extremities of Bazin and—some add—erythema nodosum of tuberculous origin
(5) The initial erythematous tuberculide of Hohmann
(6) The rosaceous tuberculide (Lewandowsky) (micropapular tuberculide of American authors)

Bolgert and Levy (1950) have criticized Darier's sub-division of tuberculosis of the skin into two groups because this suggests a sharp distinction in pathogenesis between the two they propose a classification based on anatomical structure as shown in Table I

TABLE I

BOLGERT AND LEVY'S CLASSIFICATION OF TUBERCULOSIS OF THE SKIN

Caseous tuberculoses	Ulcerative	Primary sore Secondary ulcer Atypical ulcer	
	Gummatous		
Non-caseous tuberculoses	Dermal tuberculoses	Structure roughly follicular	Verrucous tuberculosis Fungating or vegetating tuberculosis
		Structure mainly epithelioid	Lupus
		Structure more or less plainly follicular	Lichen scrofulosorum Papulo-necrotic tuberculides (Folliclis, acne scrofulosorum, acnitis) Miliary lupoid
	Hypodermic tuberculoses	Certain cases of indurative erythema and certain sarcoids Erythema nodosum of tuberculous origin	

This classification which includes sarcoid is of value since it emphasizes the variety of possible modes of reaction of the skin to the presence of the tubercle bacillus or its products

CLINICAL FEATURES

Primary tuberculosis of the skin is probably rather uncommon at least in the South of England Its characteristic features, a small persistent sore sometimes progressing to lupus, with suppurative regional adenitis, and occasionally erythema nodosum for a brief period are well known and are unlikely to be often overlooked by dermatologists In the North the condition appears to be not very uncommon Miller (1953) observed 28 cases in five years in or near Newcastle upon-Tyne. Of special interest were five cases affecting the conjunctiva the presenting symptoms were painless swelling of a pre-auricular gland and irritation in the affected eye with oedema of the eyelid Miller also observed three cases of primary ulceration

of the mouth with regional suppurative tuberculous lymphadenitis. A high proportion of the primary infections (10 out of 28 cases) was found on the lower extremities. Only one case presented with a systemic illness—a pyrexia followed measles and later the patient developed miliary tuberculosis.

A number of cases apparently of primary tuberculosis of the skin of the face and the elbows resulting from inoculation into abrasions mainly sustained in swimming pools have been reported from Sweden (Bruch, 1952 Hellerstrom, 1952). The primary sore was always associated with regional adenitis without suppuration. A mycobacterium practically indistinguishable from Koch's bacillus was isolated from some of the cases, which, however differed clinically from classical primary tuberculosis of the skin in that there was no suppurative regional adenitis. The literature is summarized by Hellerstrom who states that the problem of tuberculous and similar infections acquired in swimming-pools is complex and remains to be sol ed.

Little has been added for many years to our knowledge of the clinical features of the other forms of progressive tuberculosis of the skin Of the tuberculides, lichen scrofulosorum appears to be rare in these days and some of the younger generation of dermatologists have perhaps never seen it. Ockuly and Montgomery (1950) distinguish what they call lichenoid tuberculosis from the better known lichen scrofulosorum The condition which they describe and illustrate consists of flat topped papules, not of follicular distribution and usually occurring on the extremities. Each lesion is a little tubercle composed of endothelial cells and often with central caseating necrosis. The majority of cases are Mantoux negative. They regard the condition as a sub-group of the haematogenous forms of cutaneous tuberculosis.

Some doubt appears to exist concerning the comparative status of miliary lupus of the face of Tilbury Fox, acne agminata of Crocker and acnitis of Barthélemy In Great Britain a distinction is often made between the last named and the others, those cases in which the lesions or some of them become frankly pustular being termed acnitis while those which persist as solid discrete papules are given one of the other titles. The French apparently make no sharp distinction—Civatte in 1947 regarded lupus miliaris and acnitis as frankly identical. Degos (1953) states that when acnitis consists of solid papules as opposed to those examples which exhibit a tendency to break down, the condition approaches Tilbury Fox's miliary lupus of the face. In this group the histology is similar to that of the lichenoid tuberculide described by Ockuly and Montgomery (1950) and again some cases are Mantoux negative. It is hardly ever possible to discover any evidence of active tuberculosis elsewhere in the body in this condition or to make any noteworthy impression on its course with antituberculous chemotherapy and belief in its tuberculous origin is based on histology

The rosaceous tuberculide of Lewandowsky is usually not included in French classifications of tuberculosis. Nevertheless, the disease exists and it is well defined and recognized without great difficulty The question at issue is whether it is tuberculous or not.

The original report of Lewandowsky is quoted by Wile and Grauer (1935) as follows

The eruption on casual observation gives one the impression of rosacea not only because of its distribution over the forehead and cheeks (the nose being involved

only rarely) but also because of its reddish blue colour On close examination it is evident that the affected portions of the face are dotted by innumerable discrete lesions. The majority of these are hardly the size of a millet seed. On diascopy a faint, brownish-yellow central punctum persists in the individual papules. Microscopic examination reveals small sharply defined infiltrates made up predominantly of epithelioid cells and large giant cells centrally placed. There is no central necrosis.

Nothing further of note has been added to the clinical description of the disease about which, however a considerable literature has accumulated (Volk, 1931 MacKee and Sulzberger 1935 Wile and Grauer 1935 Pautrier and Woringer 1938 Laymon and Michelson, 1940 Laymon and Schoch, 1948 Miescher 1943 Snapp 1949 Laymon, 1951 Barber 1935 Forman 1936 Bamber 1938).

Laymon who has studied the disease closely over a number of years summarizes in a recent paper (1951) the whole of the literature. While recognizing the clinical picture as a somewhat rare entity he does not believe that a tuberculous aetiology based as it is almost purely on histology has been proven.

HISTOLOGY

It is unnecessary in the present context to consider the histological features of skin tuberculosis in any detail but some comparison of the various types of lesion in terms of histology forms a useful basis for further discussion of their bacteriology pathogenesis and response to treatment.

In lupus vulgaris the essential lesion is in the dermis and consists of few or more often many adjacent tubercles Caseation and necrosis occur but are commonly minimal although varying degrees of non-specific inflammatory cell infiltration are observed Lupus vulgaris is a disease which continues for many years, frequently with spontaneous incomplete remissions and exacerbations and there are consequently considerable variations in the histological appearances. In general however it is readily distinguished from other forms of skin tuberculosis

The primary sore in its early stages shows the non specific, acute, inflammatory reaction which is the host s initial response to a first tuberculous infection. As the host s immune and allergic reaction to the organism develop a more characteristic necrotic tuberculous lesion may be seen, and, depending on the host s ability to control the infection there may then follow complete healing, widespread dissemination or the state or balance which clinically and histologically is lupus vulgaris

Verrucous tuberculosis, like the primary lesion, resembles lupus vulgaris in that it involves the superficial layers of the dermis Histologically it differs from lupus vulgaris by presenting chiefly as a chronic inflammatory cell infiltration Typical tubercles though invariably present, are scarce and the characteristic closely packed foci of histiocytes and giant cells seen in lupus vulgaris are absent As the name implies, there is considerable epithelial hyperplasia.

The secondary ulcers and the similar skin lesions which follow the breakdown of subcutaneous tuberculous lymph nodes differ in two important respects from the conditions which have so far been considered First, they arise primarily not in the superficial layers of the dermis, but in the subcutaneous fatty tissue and

involvement of the skin is usually associated with the formation of a sinus. Secondly there is invariably considerable caseation and non-specific inflammation.

The conditions which have so far been considered have in common the fact that tubercle bacilli can be isolated from the lesions. The acceptance of sarcoid and the tuberculides as forms of tuberculosis is justified only on clinical and histological grounds for tubercle bacilli have never been recovered in these conditions.

Histologically the lesions of sarcoid may be indistinguishable from those of lupus vulgaris. The closely packed foci of histiocytes and giant cells which lie in the superficial layers of the dermis have a characteristically tuberculous appearance but the necrosis and inflammatory cell infiltrations which are found, in greater or lesser degree in lupus vulgaris, are essentially absent in sarcoid.

In lupus miliaris faciei the histology is tuberculoid, but in papulo-necrotic tuberculide of the folliclis type and erythema induratum the histological picture is much less convincing. Nevertheless, there is in all some reproduction of the characteristic cellular reaction which makes it necessary on histological grounds, to accept the possibility of a tuberculous aetiology

It will be seen that, although the majority if not all, of these lesions follow the implantation of tubercle bacilli in the skin, there are constant differences in the resulting histological patterns. On the one hand the primary and secondary ulcers show maximal necrosis and inflammation and on the other the lesions of sarcoid are characteristically free from such changes. Verrucous tuberculosis and the various types of lupus vulgaris occupy intermediate positions. The significance of this grading in terms of pathogenesis will be considered later but it is of interest in relation to the response of these lesions to calciferol. In sarcoid a satisfactory effect is occasionally observed but the results are, more commonly disappointing (Dowling and Prosser Thomas, 1946 Curtis, Taylor and Grekin, 1947 Prosser Thomas, 1950 Dowling, 1952). Similarly in those patients suffering from lupus vulgaris whose lesions most closely resemble sarcoid, calciferol is less effective than in those in whom the inflammatory and necrotic lesions are more marked. In lupus vulgaris the response to calciferol seems to vary directly with the degree of associated inflammation and necrosis (Whimster 1952).

BACTERIOLOGY

The whole group of skin lesions which have a tuberculous aetiology may be clearly divided on bacteriological grounds into two main groups. The first includes those conditions, lupus vulgaris, warty lupus, the primary and secondary ulcers, in which tubercle bacilli can be recovered from the actual lesions. The second comprises conditions such as sarcoid, lupus miliaris faciei, papulo-necrotic tuberculide, erythema induratum and erythema nodosum, which, although tubercle bacilli cannot be recovered from the lesions, are usually considered to be manifestations of tuberculosis.

Present knowledge of the nature of the organisms in skin tuberculosis is chiefly derived from the work of Griffith, who in a series of extensive investigations, isolated bacilli from a large number of patients, typed them and determined their virulence (Griffith, 1916 1916a 1919 1922).

Griffith compared strains isolated from various types of tuberculous infection and found that, although a small number of organisms from cases of pulmonary

bone and joint disease possessed atypical cultural characteristics, strains of attenuated virulence were, with rare exceptions isolated only from patients suffering from lupus vulgaris or tuberculosis of the cervical lymph nodes. These results were confirmed by Jensen and Frimodt Muller who examined 35 strains isolated from lupus lesions and found that 30 of them were of attenuated virulence (Jensen and Frimodt Muller 1936)

It is evident from the bacteriological standpoint that tuberculosis of the skin, particularly lupus vulgaris, is an almost unique form of tuberculous infection The remarkable incidence of attenuated organisms has not been explained but there



FIG. 19—Colonial morphology of virulent tubercle bacilli on Dubos albumen agar For comparison with Figs. 20 and 21 (30).

are two obvious possibilities. First lupus vulgaris may be the response of the skin to infection by an organism of previously attenuated virulence or secondly there may be initial infection with a virulent organism which becomes attenuated during the course of the disease. The principal objection to the first hypothesis is that there is a limited reservoir of attenuated strains Most patients with lupus vulgaris are infected by exposure to the usual sources of tubercle bacilli and in a study of a very large number of strains obtained from such sources Griffith observed in 1922 that very few were attenuated. This suggests that in most instances a virulent infecting strain is modified by residence in the skin, and in two patients in whom a second biopsy was taken five years after the first Griffith was able to demonstrate such a change He considered that continued exposure to light or abnormal temperature might be the responsible factor In view of the therapeutic effect of calciferol in lupus it is of interest to speculate on the possible

relationship between attenuation, exposure to light and formation of vitamin D in the skin.

Recent studies have established that tubercle bacilli possess cultural and morphological characteristics which can be correlated with their virulence (Middlebrook, Dubos, and Pierce, 1947 Gernez Rieux, Sevin and Spy 1948 Dubos, 1950). In synthetic media containing critical quantities of oleic acid esters virulent organisms produce a hydrophobic lipid substance which modifies the arrangement of dividing cells so that in fluid media they appear as solid serpentine cords of organisms and on solid media produce characteristic rough colonies (Fig. 19). Avirulent organisms which do not produce this lipid grow in a dispersed unorientated fashion in fluid media and produce distinct smooth colonies on solid media (Fig. 20). There is evidence to suggest that this lipid is actually responsible

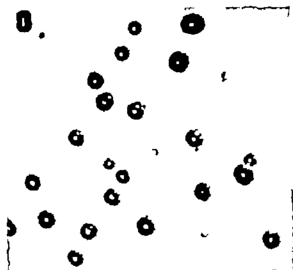


FIG. 20.—Colonial morphology of avirulent tubercle bacilli on Dubos albumen agar For comparison with Figs. 19 and 21 (30)

for the property of virulence (Allgower and Bloch, 1949) and removal of the lipid by washing with petroleum ether reduces the virulence of the organisms (Bloch, 1950). These observations indicate that the characteristics of the organism which enable it to produce progressive disease may be quite rapidly modified by changes in its physical environment. The possibility that the attenuation of virulence which follows long residence in the skin and the clinical results of calciferol therapy could both result from identical changes in the physical environment of the organisms due to local accumulation of vitamin D has been investigated (Wetherley Mein, 1952, 1953). Tubercle bacilli isolated from lupus lesions in several patients and found to be of attenuated virulence were examined by the cultural techniques of Middlebrook and Dubos and were found to possess colonial characteristics intermediate between the classical virulent and the classical avirulent strains (Fig. 21). It could therefore be assumed that during the course of the disease these strains had lost their ability to produce the lipid factor Attempts were then made to see whether similar changes could be produced in standard

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skin would be considerably increased if they could be interpreted in terms of these two essential factors. In the present context it is proposed to discuss only two aspects of this problem. First, the relationship of lupus vulgaris and warty lupus and, secondly the nature of that group of conditions, the tuberculides, from which it is rarely if ever possible to recover the tubercle bacillus.

Lupus vulgaris and warty lupus

All the lesions of warty lupus and a considerable number of the lesions of lupus vulgaris follow the exogenous implantation of tubercle bacilli in the skin. The clinical and histological features of the two types of lesion are, however consistently different and this is a fact which cannot be satisfactorily explained in terms of differences in anatomical situation. Some clue is provided by a comparison of the general age incidence of the two processes. Lupus vulgaris most commonly develops in children between the ages of 2 years and 15 years. Warty lupus is uncommon in this age-group and its initiation can usually be related to an external, often autogenous, infection of the skin in the older age-groups. In terms of immunity and tuberculin sensitivity the essential difference between individuals in these two age-groups is that in the younger group who develop lupus vulgaris the cutaneous inoculation of tubercle bacilli must frequently be their first encounter with the organism while in the older group particularly in urban communities, the majority of individuals who develop warty lupus have been, to some degree already immunized and sensitized by the commoner primary pulmonary or alimentary lesions. These observations suggest that the local skin immunity to tuberculous which develops in the individual whose primary infection is in the skin itself differs considerably from the skin immunity of the individual whose primary infection is, for example, in the lung or the gut. This implies that lupus vulgaris will only develop in those individuals in whom the primary tuberculous infection is in the skin. Warty lupus will, on the other hand, follow tuberculous re-infection of the skin in individuals who have been previously immunized by a primary pulmonary or alimentary infection.

This explanation is, of course, no more than a hypothesis, but it is supported by the well-recognized observation that a not infrequent sequel of a recognized primary skin complex is the development of lupus vulgaris at the site of inoculation.

The tuberculides

When the group of conditions classified as tuberculides is considered it is evident that if the criteria of classical pathology are applied to these processes the term is quite appropriate, for there is no satisfactory evidence that they contain tubercle bacilli and, in spite of their clinical and histological features, their tuberculous aetiology must be suspect. Further the histological evidence is of limited value for it is evident that the body has only a limited repertoire of cellular reaction and the histological pattern of tuberculosis may be produced in response to a wide variety of non-tuberculous stimuli. Clinically however the close association of a number of these lesions, such as the papulo-necrotic tuberculide, with established tuberculous lesions elsewhere in the body suggests very strongly that their nature is in fact tuberculous. In spite of the fact that these lesions do not contain tubercle bacilli, modern concepts of immunity and cellular reactions in tuberculosis may be reasonably invoked to support the clinical concept of their tuberculous

virulent tubercle bacilli by prolonged *in vitro* exposure to calciferol. Strains were subcultured in the presence of calciferol for up to two years but no modification of colonial morphology or animal virulence was effected. The mechanism of attenuation is, therefore, still obscure, but the studies of Griffith, Jensen and Frimodt Muller clearly establish that the skin provides an unfavourable environment for the tubercle bacillus and this is, obviously, an important factor in the pathogenesis of skin tuberculosis.

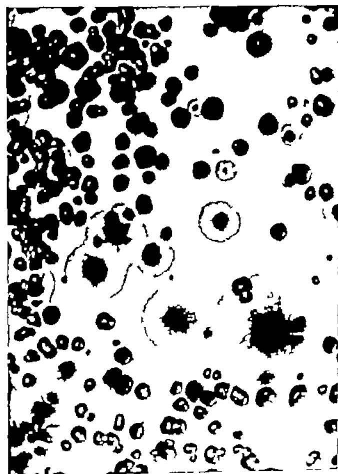


FIG. 21.—Colonial morphology of an attenuated lupus strain of tubercle bacilli on Dubos albumen agar. Showing avirulent and intermediate type colonies. (× 30)

PATHOGENESIS

The essential factors which determine the course of any tuberculous infection are first, the number and virulence of the infecting organisms and, secondly, the reaction of the host to the particular infection. This general principle has been fully discussed by several authors (Rich, 1946; Dubos, 1950; Lurie, 1950; Medlar, 1950) and need not be elaborated here. The reaction of the host, which is presumably conditioned by environment and genetic constitution, comprises two distinct elements—immunity, which can only be measured statistically, and tuberculin sensitivity, which can only be crudely measured in the individual by such tests as the Mantoux reaction.

Understanding of the wide variety of processes grouped as tuberculosis of the

others. Dowling and Prosser Thomas's first case developed acute inflammatory congestion of his lupus a few weeks after treatment had begun early aggravation of symptoms together with gradual increase in the intensity of the reaction to tuberculin was observed frequently by Macrae (1947) on a group of 20 hospitalized cases of lupus. Subsequently many authors have reported on the occasional occurrence of exacerbation in the lupus, and the appearance of tuberculous manifestations elsewhere on the skin or in other organs (Green 1947 Nekam, Kovacs and Farago 1947 Simon, 1947 Grzybowski and Miedzinski 1950 Marcussen and Nielsen, 1952 Riehl, 1952).

Subsequent observation of patients over a period of 10 years has shown that gradual relapse occurs frequently but that the disease can usually be brought under control by further treatment.

Marcussen and Nielsen (1952), in a report concerning 280 cases of lupus treated with calciferol alone for 3 5 years, made the following observations during the first course of treatment, histologically verified inactivity was obtained in 83 5 per cent. Treatment beyond 34 months did not add to the number of symptom-free patients. A systematic tendency to recurrence was demonstrated and it was therefore reasonable to suppose that the majority of calciferol-treated patients would suffer relapse within a limited observation period. At the end of the experimental period only 33 per cent of the patients remained symptom-free after one course of treatment. Signs of a spread or flare up of the tuberculous process were demonstrated in 15·4 per cent, in 11 1 per cent of these in previously unaffected areas. More than half of these occurred in organs other than the skin. Comparison with Finsen treatment showed that transitory freedom from symptoms seemed to be obtained in a considerably higher percentage by calciferol than by the Finsen light. The Finsen treatment, however was limited by the fact that in practice it is impossible to obtain freedom from symptoms in the most extensive cases. Marcussen suggests that the fundamental difference between the two forms of treatment might be explained as follows calciferol acts on the tuberculous tissue without having a bacteriostatic or bactericidal effect, so that the liberated bacilli may stay in the body and may produce local recurrence or fresh tuberculous processes. On the other hand Finsen treatment gives a purely cosmetic result without affecting the balance of the tuberculous infection.

Dangers associated with treatment with calciferol

It has always been known that calciferol in large doses provokes in many patients a number of toxic symptoms, and these have been brought forcibly to the notice of many during the treatment of lupus. They are, in the order of frequency and severity malaise, headache, indigestion, anorexia, thirst, and polyuria, constipation, loss of weight, nausea and vomiting, photophobia and coma. These symptoms are perhaps, always associated with some degree of hypercalcaemia and soon disappear with the cessation of treatment or reduction in dose. Ingram, Anning and Dawson (1948) drew attention to the more serious possibility of causing permanent or at least very prolonged renal damage by this treatment.

Following the publication of the work of these authors, Dowling, Gauvain and Macrae (1953) subjected all cases of lupus and tuberculous adenitis under treatment with calciferol to routine tests for renal efficiency and estimated blood calcium levels before treatment, at monthly intervals during treatment and after its

nature The work of Sabin and others (Sabin, 1938 Smithburn and Sabin, 1938 *Ungar Coulthard and Dickinson 1945*) established that dead tubercle bacilli or chemical fractions of tubercle bacilli are capable of evoking cellular reactions often distinguishable from the lesions produced by live organisms only by their tendency to spontaneous regression Lurie s studies on the bactericidal activity of monocytes indicate that in the immune and sensitized host these cells have an increased capacity for the *phagocytosis and destruction of living tubercle* bacilli (Lurie, 1939 and 1942) On the basis of this evidence it is possible to suggest that in, for example, the papulo-necrotic tuberculide the skin is involved as a result of blood-stream dissemination of living or degenerate tubercle bacilli derived from some separate tuberculous focus If under these circumstances the local immunity of the skin is adequate and the numbers of organisms are not overwhelming, it is reasonable to assume that the implanted tubercle bacilli will be fairly rapidly phagocytosed and destroyed By virtue of their chemical composition they will, *however still be capable of evoking the classical cellular response* with, possibly an associated non specific inflammatory reaction The lesion will at this stage, therefore, have many if not all of the histological features of tuberculosis, will contain no viable tubercle bacilli and will, consequently regress spontaneously It will in fact have the essential characteristics of the papulo-necrotic tuberculide. If the remaining conditions in this group are examined in this light it is possible to construct logical hypotheses which will explain their structure and clinical behaviour in terms of fundamental pathology

The skin is evidently an organ which from an immunological point of view is capable of developing a variety of specific and independent patterns of reaction to various stimuli With the exception of certain conditions, such as the rosaceous tuberculide, which are possibly not tuberculous at all it seems reasonable to regard the whole group of tuberculous and tuberculide lesions as manifestations of varying *states of skin immunity and sensitivity to the tubercle bacillus.*

TREATMENT

In Great Britain lupus appears to be a slowly vanishing disease. It was never very common but patients were not often completely cured of it and many attended the large general hospitals for many years, some for the greater part of their lives The reason for the change is perhaps partly due to a decrease in the incidence of *the disease, but no doubt principally to the employment* of calciferol in massive doses in treatment, introduced by Charpy (1943) in France during World War II and by Dowling and Prosser Thomas (1945) in Great Britain It is interesting to note that the dosage found by trial and error to be effective was about the same in both countries and has hardly been modified since that is an initial loading dose of about 150 000 international units daily for about a month followed by sustained treatment with 100 000 international units daily for a year or more. The results were impressive and it appeared that the problem of lupus was on the way to solution *The costly equipment* and labour which the treatment of lupus had hitherto demanded appeared to be no longer necessary Vachon and Feroldi (1945) first hinted at the probability of relapses by drawing attention to the fact that histological cure was not always obtained even when *the patient appeared to be* clinically symptom free. Their observations were later confirmed by Joppe (1950) and by

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TABLE II

RENAL CLEARANCE IN RELATION TO BLOOD CALCIUM LEVELS—ADULTS

(*Dowling Gauvain and Macrae 1953*)

Average urea clearance below 100% normal average	*Highest blood calcium in mg per 100 ml* 9–10	10–11	11–12	12–13	13–14	14–15	15–16	16–17	17–18	*Totals*	*Renal efficiency when followed up (1952)* *Impaired*	*Unimpaired*	*N t yet followed up*
−90%	–	–	1	–	–	1	–	1	–	3	3	–	–
−75%	–	–	–	–	–	–	3	–	–	3	1	2	–
−60%	–	1	1	3	2	3	–	1	–	11	4	5	2
−45%			7	1	2	2	–	1	–	15	7	6	2
−30% (Normal)	–	1	1	–	1	–	–	–	–	3	–	2	1
−15% (Normal)	1	4	5	1	3	–	–	–	–	14	–	14	–
Totals	1	8	15	5	8	6	3	3	0	49	15	29	5

completion. Nearly 100 cases were studied and followed up for a year or more after the completion of treatment. 47 of these were children and 49 were adults. Of the 47 children, 30 were investigated for evidence of renal impairment during the course of treatment. In 13 cases some degree of impairment developed, 2 showing at one time less than 40 per cent of normal average urea clearance. At the follow up of these 13 cases the urea clearance was found to be normal in all except one whose renal function was very slightly impaired. Of the remaining 17 five of whom developed clinical toxicity during treatment, slight impairment of function was found in one who showed a urea clearance value of 66 per cent 2 years after completion of treatment.

Of the 49 adults, 32 showed varying degrees of impairment of renal efficiency during treatment. In the final assessment, renal function remained impaired in 15 and 5 patients were not traced or declined the investigation. The relationship of the blood calcium levels to urea clearance values is illustrated in Table II. This indicates that while comparatively low gross calcium levels may be associated with impairment of renal function, the kidneys are almost certain to suffer damage when high levels are attained.

Table III illustrates the incidence of clinical toxicity in relation to blood calcium levels in children and adults. It has often been stated that clinical toxicity and

TABLE III

Clinical Toxicity in Relation to Blood Calcium Level

(Dowling, Gauvain and Macrae, 1953)

A—*Adults*

Toxicity	*Highest blood calcium level in mg. per 100 ml.* 9–10	10–11	11–12	12–13	13–14	14–15	15–16	16–17	17–18	18–19	Totals
			1		2	4	2	3			12
		1				2					3
		1	1		2						4
		1	1		2	1					5
Non-toxic	1	5	11	5	3						25
Totals	1	8	14	5	9	7	2	3	0	0	49

B—*Children*

										–	0
				2			1	1		1	5
			2		2	2	1				7
Non-toxic		10	12	3	2	1				–	28
Totals	0	10	14	5	4	3	2	1	0	1	40

Very slight symptoms, sometimes ? attributable to the drug.
Malaise, headache, indigestion, anorexia, sometimes thirst and polyuria, tendency to constipation.
All the above, and loss of weight, nausea and vomiting.
+ All the above more marked, with on occasion even photophobia and coma.

hypercalcaemia are unrelated. The Table shows that 18 out of 24 adults who exhibited intolerance developed blood calcium levels over 13 milligrams per cent while in 6 cases the blood calcium was found to be 12 milligrams per cent or less. In 10 out or 12 children who exhibited clinical intolerance the blood calcium levels exceeded 12 milligrams per cent.

In all patients the blood calcium levels were estimated at monthly intervals, sometimes a few weeks after the onset of toxic symptoms. The levels sometimes dropped quite rapidly after treatment was stopped—as it always was when toxicity developed—and it is possible that some of the figures obtained may have been lower than those present at the time of maximal toxicity On the whole the findings suggest that while toxicity is in fact related to the disturbance in calcium metabolism produced by calciferol in large doses such disturbance does not necessarily produce toxic symptoms in all patients. On the other hand toxicity appears to be unrelated to renal impairment While toxic symptoms disappear rapidly on the cessation of treatment, evidence of renal impairment persists usually for some months Table IV shows that 6 out of 13 children, and 11 out of 29 adults who suffered renal damage, exhibited no sign of toxicity at any time.

TABLE IV

CLINICAL TOXICITY COMPARED WITH RENAL EFFICIENCY

(Dowling Gauvain and Macrae 1953)

A—*Adults*

Urea clearance below 100% average normal	*Clinical toxicity*					*Totals*
	0	±	+	+ +	+ + +	
90%	–	–	–	–	2	2
-75%	1	–	–	–	3	4
60%	3	–	1	–	6	10
-45%	7	2	–	3	1	13
-30% (Normal)	3	2	2	–	–	7
-15% (Normal)	11	2	–	–	–	13
Totals	25	6	3	3	12	49

B—*Children*

	0	±	+	+ +	+ + +	Totals
-75%	1	–	1	–	–	2
-60%	–	–	–	–	1	1
-45%	5	2	3	–		10
-30% (Normal)	8	1	–	–	–	9
-15% (Normal)	4	1	2	1		8
Totals	18	4	6	1	1	30

0 – No toxic symptoms.
± – Very slight symptoms, sometimes ? attributable to the drug.
+ – Malaise, headache, indigestion, anorexia, sometimes thirst and polyuria, tendency to constipation.
+ + – All the above, and loss of weight, nausea and vomiting.
+ + + – All the above more marked, with on occasion even photophobia and coma.

Thus it is clear that the use of calciferol in the doses required for the treatment of lupus is not without danger. It always appears that its danger lies in the hypercalcaemia to which it may give rise and which, owing to deposition of calcium in the renal tubules, may cause damage to the kidneys. Toxicity is associated closely with hypercalcaemia, but its mechanism is not established.

Combined streptomycin and vitamin D

Vitamin D will not suppress lupus completely in all patients. In order to overcome the frequent halt in progress after initial improvement, Cornbleet (1948) treated seven cases with both vitamin D and streptomycin, the antibiotic being given after some months of treatment with vitamin D alone. All patients made excellent further progress on the combined treatment. The dose of streptomycin was 1 gramme daily and it was continued for 6–9 weeks. In all cases the tuberculous lesions appeared to be clinically cured. Cornbleet stated that streptomycin alone did not appear to be helpful in the treatment of lupus. These observations were confirmed by Craps, Lapère and van Runckelen (1952).

Thiosemicarbazone

This drug, developed in Germany, has been little used in Great Britain. Several authors (Joel, 1949; Kalkoff, 1949) found it valuable but on the whole less reliable than calciferol.

Isonicotinic acid hydrazide (isoniazid)

This, the most recent of the anti-tuberculous drugs, has been in use in Great Britain for about 18 months. Dowling and his colleagues (1953) and Dowling and Seville (1953) reported on 16 cases treated with isoniazid for 4–5 months. All except two of these had previously received calciferol for a prolonged period and had either relapsed or proved resistant to the treatment. Some had also been treated in addition with streptomycin and with thiosemicarbazone. The dosage was from 3 to 6 milligrams per kilogram of body-weight. All the patients with the exception of one, in whom treatment was abandoned because of toxic effects, showed well-marked improvement within a month. After 2 months only 2 cases showed any clinical evidence of activity. Toxic effects occurred in 4 patients, one developing severe vertigo and a coarse tremor of the hands which persisted even with a dose of 50 milligrams daily.

Russell and Thorne (1953) reported progress on 15 cases who had been treated for periods varying from 9 to 30 weeks. All had made quiet but steady progress on the dose of 300–400 milligrams daily. Russell and Thorne made no mention of toxicity.

Sommerville and Milne (1953) reported 26 cases treated in the same way for periods of 7–32 weeks, of which not one failed to show continued improvement. They noticed toxic effects in 5 cases but this did not apparently call for the cessation of treatment. Braun-Falco and Rathjens (1953) have treated 67 cases of cutaneous tuberculosis, chiefly lupus, with isoniazid and conclude that the results of treatment appear earlier and are more rapid than with calciferol.

Thus it seems clear that isoniazid is a more rapidly effective remedy than

hypercalcaemia are unrelated. The Table shows that 18 out of 24 adults who exhibited intolerance developed blood calcium levels over 13 milligrams per cent while in 6 cases the blood calcium was found to be 12 milligrams per cent or less. In 10 out or 12 children who exhibited clinical intolerance the blood calcium levels exceeded 12 milligrams per cent

In all patients the blood calcium levels were estimated at monthly intervals, sometimes a few weeks after the onset of toxic symptoms The levels sometimes *dropped quite rapidly after treatment was stopped—as it always was when toxicity* developed—and it is possible that some of the figures obtained may have been lower than those present at the time of maximal toxicity On the whole the findings suggest that while toxicity is in fact related to the disturbance in calcium metabolism produced by calciferol in large doses such disturbance does not necessarily produce toxic symptoms in all patients On the other hand toxicity appears to be unrelated to renal impairment. While toxic symptoms disappear rapidly on the *cessation of treatment, evidence of renal impairment persists usually for some* months. Table IV shows that 6 out of 13 children, and 11 out of 29 adults who suffered renal damage exhibited no sign of toxicity at any time.

TABLE IV

Clinical Toxicity Compared with Renal Efficiency

(Dowling Gauvain and Macrae 1953)

A—*Adults*

Urea clearance below 100% average normal	Clinical toxicity 0	±	+	+ +	+ + +	Total
90%	–	–	–	–	2	2
–75%	1	–	–	–	3	4
–60%	3	–	1	–	6	10
–45%	7	2	–	3	1	13
–30% (Normal)	3	2	2	–	–	7
–15% (Normal)	11	2	–	–		13
Totals	25	6	3	3	12	49

B—*Children*

	0	±	+	+ +	+ + +	Total
–75%	1	–	1	–	–	2
–60%	–	–	–	–	1	1
–45%	5	2	3	–		10
–30% (Normal)	8	1	–	–	–	9
–15% (Normal)	4	1	2	1		8
Totals	18	4	6	1	1	30

0 – No toxic symptoms.
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1952, 1953). Stringer's observations on the effect of calciferol on phthioic acid granulomas lends further support to the belief that it acts in lupus by stimulating the reaction of the host. Phthioic acid is one of the lipid constituents of the tubercle bacillus which, when inoculated into the skin, provokes a cellular reaction comparable to that produced by the tubercle bacillus itself (Ungar Coulthard and Dickinson, 1948). Stringer (1948) found that parenteral administration of calciferol enhanced the repair of these granulomas and induced a cellular response similar to that produced in treated lupus. Jensen's (1948) clinical studies on the effect of local injection of vitamin D in lupus suggest that the results of parenteral therapy are due to the local accumulation of vitamin D itself This is confirmed by the more recent experimental investigation of the mode of action of the Finsen lamp by van der Lugt (1952)

All the available evidence therefore indicates that calciferol itself has no direct effect on the tubercle bacillus, but that in the treated patient there is a local accumulation of vitamin D in the skin which results in a stimulation of the cellular reaction of the host to the chemical fractions of the tubercle bacillus.

The fact that two effective forms of therapy calciferol and the antibacterial agents, have entirely different modes of action is of some practical significance. The antibacterial therapy of any form of tuberculosis is sooner or later complicated by the development of drug-resistant strains of tubercle bacilli. This difficulty is to some extent overcome by some form of combined therapy and two or more antibiotics may be used simultaneously The distinct modes of action of calciferol and antibacterial chemotherapy suggest that, in spite of the dramatic results which are now being obtained with isoniazid in the treatment of lupus, there may in the future be a place for calciferol in the combined therapy of drug-resistant cases There is already some evidence that calciferol and the antibacterial agents are *synergistic*. The effect of calciferol appears to be enhanced by the administration of thiosemicarbazone, *para*-aminosalicylic acid or *streptomycin* (Cornbleet, 1948 Riehl, 1952 Sainz de Aja, 1952) and Craps Lapière and Van Runckelen (1952) found that although calciferol or a combination of calciferol and streptomycin might be curative streptomycin alone was ineffective.

The mode of action of the Finsen lamp in lupus vulgaris has recently been investigated by van der Lugt (1952) of the Finsen Institute in Rotterdam and he has very kindly made his unpublished observations available. He has shown, very convincingly that the Finsen lamp produces its effect by increasing the local concentration of vitamin D If ergosterol is injected into part of a lupus lesion it produces no change. If the whole lesion is then irradiated with ultra-violet light in doses which would normally be ineffective, healing occurs only in the area which contains ergosterol If the experiment is repeated and light of the wavelengths necessary to convert ergosterol to calciferol is excluded by filters, healing does not occur

It is evident that the actions of calciferol and the Finsen lamp are of the same order and that both produce their effect by increasing the local concentration of vitamin D with consequent stimulation of the host's specific cellular reaction to the tubercle bacillus.

These findings, the results of calciferol therapy and the rarity of skin tuberculosis in populations which are continually exposed to the sun (Molesworth, 1928 Marchionini, 1944) indicate that the formation of vitamin D in the skin is an

calciferol and more uniformly reliable It will no doubt be used in combination with streptomycin as advocated by Joiner and his colleagues, or with calciferol. The relapse rate will not be known for some while.

Local treatment

Owing to the simplicity of the treatment of lupus with calciferol and other chemotherapeutic remedies, local treatment of lupus has probably been somewhat neglected in recent years Yet the need for local treatment is now even greater than formerly when only cases of limited extent could be helped. Gauvain at the Lord Mayor Treloar Hospital and Macrae, at the Morland Clinics at Alton, have continued to treat all cases of lupus controlled by calciferol or isoniazid, with either the Finsen light or the Kromayer lamp combined with the application of picric brass paste (basic copper sulphate 85 per cent zinc sulphate 14 per cent, picric acid 1 per cent) or with brass paste alone. Macrae (1953) has observed that picric brass paste has proved more effective as a selective caustic in lupus treated with isoniazid than with calciferol histological comparison of the lesions treated by the two methods offers a reasonable explanation of the difference.

The mechanisms of effective forms of treatment

It is of interest to compare the modes of action of the main types of therapy which are effective in the treatment of skin tuberculosis particularly lupus vulgaris. [illegible]

tuberculosis. The considerable variations in clinical response to different anti bacterial substances probably depend on two factors First, ability of the particular drug to penetrate and accumulate in the lesion, and secondly the degree to which perpetuation of the particular lesion depends on the presence of viable tubercle bacilli rather than on some abnormal immunity reaction of the host.

The most significant result of recent studies of the clinical and histological changes associated with effective chemotherapy particularly isoniazid is that they differ very considerably from the changes which follow the successful administration of calciferol The differences are sufficiently marked to suggest that the modes of action of these two forms of treatment are fundamentally dissimilar With isoniazid there is resolution of the tubercles with minimal histiocytic activity (Milne 1953 Whimster 1953) With calciferol the primary and essential change is increased fibroblastic activity with only secondary replacement of the tubercles with scar tissue (Vachon and Feroldi 1945 Freudenthal 1948)

Studies of the mechanism of action of calciferol in lupus confirm this hypothesis. Prolonged and repeated subculture of standard virulent and of attenuated lupus strains in the presence of calciferol showed that their growth viability and virulence were unaffected by calciferol This indicated that calciferol does not act as a bacteriostatic or bacteriocidal agent and suggested that it acts by stimulating the reaction of the host to the organism. Further investigation showed that it has no effect on the repair of experimental non tuberculous skin lesions and confirmed the clinical impression that its action is specifically anti tuberculous (Wetherley Mein,

1952, 1953). Stringer's observations on the effect of calciferol on phthioic acid granulomas lends further support to the belief that it acts in lupus by stimulating the reaction of the host. Phthioic acid is one of the lipid constituents of the tubercle bacillus which, when inoculated into the skin, provokes a cellular reaction comparable to that produced by the tubercle bacillus itself (Ungar, Coulthard and Dickinson, 1948). Stringer (1948) found that parenteral administration of calciferol enhanced the repair of these granulomas and induced a cellular response similar to that produced in treated lupus. Jensen's (1948) clinical studies on the effect of local injection of vitamin D in lupus suggest that the results of parenteral therapy are due to the local accumulation of vitamin D itself. This is confirmed by the more recent experimental investigation of the mode of action of the Finsen lamp by van der Lugt (1952).

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he was not able to identify them as such. He added "In accordance with the histological findings it is likely that, if the disease is due to some parasite, it will be found to be lodged in other organs than the skin, for example in the glands or also in the blood. The glands were not, however examined and I have not succeeded in demonstrating any parasite in the blood." Boeck maintained that the swelling of the glands could hardly be a result of the skin disease, and he continued "To what extent could similar changes perhaps also exist in other organs without being clinically demonstrable is a question to which no answer can be given for the moment." He concluded his first communication by stating that "on further investigation this condition may prove to be connected with the pseudoleukaemias."

In his first publication, Boeck pointed out that in 1896, at the International Dermatological Congress in London, he had seen a case similar to the one he had now described, and he added that "several of the most experienced members of the Congress had never seen the disease, and no one knew anything to say about its character I had not myself at the time examined it histologically"

Boeck mentioned Jonathan Hutchinson's description of "Mortimer's malady" published in 1898, and maintained that it was a case of the same disease (Hutchinson referred to his case as "lupus vulgaris multiplex non-ulcerosus et non-serpiginosus") In several later works, up to 1916, Boeck dealt with the clinical manifestations of this disease the aetiology of which he tried to discover It will thus be seen that he not only described sarcoid in the skin, but also discussed its localization in the lymphatic glands, the nasal mucosa, the conjunctiva and the lungs. He referred to the existence of certain cytological changes in the blood (an increase in the number of the large monocytes), and gave a detailed account of the histology of the cutaneous lesion. He stressed repeatedly in his works that he was dealing with a "general disease" As early as 1905 he maintained that the disease is "ein tief in dem Organismus wurzelndes Leiden." He came gradually to the conclusion that the malady must be regarded as a "variety of tuberculosis" *In spite of his having* from the outset used the unfortunate term "skin sarcoid" —which he subsequently changed to "benign miliary-lupoid"—it must be obvious that he not only described a disease of the skin, but one which involved several internal organs. It is therefore incorrect to limit Boeck's name only to the cutaneous manifestations of the disease while other names are linked with other descriptions indicating the general character of the disease,—"lymphogranulomatosis benigna for example.

In a correspondence in connexion with an English doctor's employment of the term Boeck's disease (sarcoid)" Schaumann (1935) remarked *inter alia* "that it would be better in accordance with actual facts to say that Besnier's lupus pernio, Boeck's sarcoid and Schaumann's forme érythrodermique du lymphogranulome bénin represent different aspects of the same disease, namely of lymphogranulomatosis benigna which, in 1914 I described as a disease generalized—with or without skin lesions—in the lymphatic glands, the tonsils, the bone marrow the spleen and liver and lungs."

With a malady such as sarcoidosis, capable of presenting so many characteristic features, it is natural to find various descriptions of one and the same disease in medical literature. Besnier's description (1889) of "lupus pernio" is particularly interesting. Kienbock (1902) described curious radiological changes in the

CHAPTER 8

SARCOIDOSIS

NIELS DANBOLT

INTRODUCTION

IN RECENT YEARS, sarcoidosis (Boeck's sarcoid, Besnier Boeck-Schaumann's disease) has attracted much attention. This is so first because the disease seems to be capable of provoking manifestations from practically every system of organs with the result that doctors, whatever their speciality may be, are obliged to keep the possibility of this diagnosis in mind secondly because the aetiology of the malady is unknown, and the disease offers vistas of both clinical and experimental research, and encourages speculation

In this chapter no attempt will be made to deal with all the clinical manifestations and symptom-complexes which with more or less justification are regarded as expressions of sarcoidosis. Nor will any attempt be made to present a complete bibliography My primary object is to present a survey of the more recent clinical and laboratory investigations which are capable of illuminating the aetiology of sarcoidosis. As some of these investigations have been carried out in my hospital department, it has seemed natural to present a brief account of cases of sarcoidosis which have been kept under periodic hospital or out patient observation in the course of the last 10 years. Certain characteristic case records will be reviewed to serve as a background for my main objective. Finally I shall consider modern views concerning the aetiology of sarcoidosis, its diagnosis, treatment and prognosis.

CERTAIN FEATURES OF THE HISTORY OF THE DISEASE

At a meeting of the Norwegian Medical Society in Christiania in 1897 Professor Caesar Boeck demonstrated a patient presenting "a form of disease which, as far as I know has not hitherto been described and which is most curious from both the clinical and anatomical points of view" He called this disease "multiple, benign skin-sarcoid An account of this case was first published in Norway and later in 1899 in a somewhat modified form in the United States of America. The patient was a man aged 36 years, who had developed multiple infiltrations in the skin in the course of some years He also presented swelling of the superficial lymphatic glands, the epitrochlear glands being particularly large. A leucocytosis was present the number of large monocytes was particularly striking. Boeck studied the histo-pathology of the cutaneous infiltrations, and described compact, sharply-defined tumour foci" permeating the corium. These foci consisted of epithelioid connective tissue cells with large pale nuclei some giant cells were present. Boeck also described some granules in a part of the protoplasm of the cells, and he pointed out the very close resemblance of these granules to cocci

TABLE I

AGE DISTRIBUTION OF THE HOSPITAL'S SARCOIDOSIS MATERIAL (PATIENTS OBSERVED IN HOSPITAL IN THE PERIOD 1943–1952)

Age at first onset of the symptoms according to the patient's own statements (years)	*Number of patients*			*On first admission to hospital*	*Number of patients*		
	Males	Females	Total		Males	Females	Total
0–10	1	0	1	0–10	1	0	1
11–20	0	2	2	11–20	0	0	0
21–30	7	5	12	21–30	3	4	7
31–40	7	10	17	31–40	5	3	8
41–50	8	12	20	41–50	12	15	27
51–60	2	6	8	51–60	5	8	13
61–70	1	0	1	61–70	0	5	5
	26	35	61		26	35	61

It should be noted that the majority of the patients (42 out of 61) belonged to the sexually mature age but 18 of the 61 were over the age of 50 years when first admitted to hospital.

Sarcoidosis is relatively rare in childhood among the white races the following brief history of the youngest case is therefore of interest.

Case I Per J aged 9 years. General condition good. Some 20 brownish nodules from the size of a grain of corn to that of a bean were scattered over his face. They were flat, slightly prominent, to some extent presenting a lightly scarred centre. Scanty desquamation. Nothing else abnormal found on clinical examination. Duration of the disease about 6 months.

Report of histological examination of an excised nodule "Differentiated reaction. Boeck's sarcoid probable."

Report of x-ray examination of the thorax "Slightly enlarged, dense hilar shadows on both sides. Possibility of enlargement of the paratracheal glands."

Pirquet and Mantoux (1 mg.) tests, negative. The diagnostic BCG reaction "Negative early-reaction." Wassermann negative. Normal findings on cytological blood examination. Kveim's test positive with one antigen, negative with two other antigens. Local Finsen treatment, moderate calciferol treatment. The boy's father subsequently stated that the infiltrations disappeared in the course of a year. Since then he has been perfectly well.

Commentary This 9-year-old boy had a finely-nodular form of Boeck's sarcoid situated in the skin, with enlargement of the mediastinal glands. The clinical picture combined with the histological findings, the negative tuberculin reactions and the positive Kveim reaction confirmed the diagnosis which was further supported by the benign course of the disease.

Table II presents the most important manifestations of sarcoidosis in the present material. It will be seen that in 53 of the 61 cases there were cutaneous lesions the frequency with which these were noted is connected with the fact that the material hails *from a dermatological department*. It is impossible to say with

fingers of patients suffering from lupus pernio Kreibich (1904) concerned himself with the same condition. But the best known is Jüngling's work in 1919 on these changes in the bones described as "osteitis tuberculosa multiplex cystica"

In a series of publications, Schaumann (1917 1924 and 1934) made valuable contributions to our conception of sarcoidosis. In 1914 he wrote a prize essay "Sur le lupus pernio which was first published in 1917 Here he proved that lupus pernio and Boeck's sarcoid are the same disease. He showed that the characteristic histological changes are also to be found in lesions in the tonsils and in the bone marrow He emphasized the significance of the pulmonary lesion, and he maintained that it can exist without simultaneous manifestations in the skin. He taught that the disease is concerned with the lymphatic tissues, and he suggested the term lymphogranuloma benignum

It is impossible to consider here many of the recent publications on sarcoidosis. It must suffice to mention several large monographs with extensive bibliographies *Pautrier (1940) Gravesen (1942) Leitner (1942) Longcope and Freiman (1952),* Jaques (1952) Gougerot (1947) published a survey of the many clinical manifestations which are supposed to be expressions of the disease. Vosbein and Bonnevie (1947) considered its cutaneous manifestations.

Several distinguished scientists have studied this disease, and the first to be mentioned are the pioneers Boeck, Besnier and Schaumann. There is therefore much to be said for the name, adopted by many Besnier Boeck-Schaumann's disease *It would, however seem to be more convenient to employ the simpler* term sarcoid as originally suggested by Boeck himself or to adopt the word sarcoidosis which emphasizes the general character of the disease more effectively This term is now much employed in Anglo-Saxon publications and will be used in the present survey

CLINICAL MANIFESTATIONS

Sarcoidosis is a systemic disease which makes its appearance in the form of a "reticulo-endothelial tissue reaction which can occur in various organs and therefore gives rise to very varied clinical manifestations.

As already stated no attempt will be made to give a detailed description of the *clinical features of sarcoidosis. As account will however be given of* a series of 61 patients suffering from sarcoidosis who in the course of the last 10 years have been admitted to this hospital department, and who have thus been subject to prolonged observation. In the hospital's out patient department a still greater number of patients have been examined they are not, however dealt with here. A short account *will be given of the most important localizations of the disease* in this hospital material, and of the results of special examinations found to be timely or opportune. The results of these clinical and laboratory examinations will then be reviewed in a later section as they seem to be of significance to the evaluation of the aetiology of sarcoidosis.

Of the 61 sarcoidosis patients, 26 were males and 35 females. *Table I gives the* ages supplied by the patients themselves of the first appearance of symptoms. Most of the patients were between the ages of 20 and 50 years, and most of them were between the same age limits when they were admitted to hospital

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The "diagnostic BCG test" described by Ustvedt and Aanonsen (1949) was performed on 29 sarcoidosis patients, and the results are shown in Table IV

TABLE IV

The Results of the "Diagnostic BCG Test" in 29 Sarcoidosis Patients Compared with the Outcome of the Tuberculin Test

	Negative early-reaction	*Positive early-reaction*
21 patients with Pirquet-negative Mantoux-negative	19	2
5 patients with Pirquet-negative Mantoux-positive	3	2
3 patients with Pirquet-positive Mantoux-positive	2	1
29 patients	24	5

Among 21 cases which were also tuberculin-negative, 19 failed to give an early reaction to the BCG test. In the remaining 2 cases the patients were tuberculin-anergic and gave a "positive early reaction" indicative of an existing allergy to tubercle bacilli. Among 5 Pirquet-negative but Mantoux positive patients were 3 who gave a "negative" and 2 a "positive early reaction" Of 3 patients who were positive to both Pirquet and Mantoux tests, 2 gave a negative and 1 gave a positive BCG reaction. This test of tubercle bacillus allergy has on the whole yielded results similar to those from the tuberculin tests. It is, however interesting to note that 5 of the Mantoux-positive sarcoidosis patients, that is tuberculin-allergic patients, did not react to the "diagnostic BCG test" This finding suggests that the positive Mantoux reactions may perhaps have been non-specific. According to Ustvedt and Aanonsen (1949) it may be assumed that the diagnostic BCG test is a more accurately delicate reaction to tuberculosis than a tuberculin test. Among the 29 sarcoidosis patients to whom BCG cutaneous tests were applied were at least 11 reacting with definite late papules (appearing several weeks after the inoculation). These papules were examined histologically (*see* p 139).

Kveim's reaction was carried out on all the sarcoidosis patients with results which are given in Table V

TABLE V

Kveim's Reaction in 61 Sarcoidosis Patients

Results	*Males*	*Females*	*Total*
Positive	21	28	49
Faintly positive ("doubtful positive")	2	3	5
Negative	3	4	7
Total	26	35	61

certainty what proportion of cases of sarcoid have cutaneous lesions. It is only in the most recent years that it has become quite obvious that sarcoidosis is very often limited to the internal organs.

TABLE II

CLINICAL MANIFESTATIONS IN 61 SARCOID CASES OBSERVED IN HOSPITAL

Clinical manifestations involving	*Males*	*Females*	*Total*
The skin	19	34	53
The glands	18	12	30
The lungs and pulmonary glands	24	19	43
The bones	6	11	17

Demonstrable enlargement of the superficial lymphatic glands was found in 30 of the 61 cases. A radiological examination showed in 43 cases either enlargement of the hilar glands and paratracheal glands with or without bilateral parenchymal opacities in the lungs without demonstrable enlargement of the glands—pulmonary changes which experienced radiologists interpret as being sarcoidosis-suspect In many cases there were demonstrable changes in both the mediastinal glands and in the lung parenchyma. In 17 of the 61 cases, a radiological examination showed cystic lesions in the bones of hands or feet (osteitis cystoides).

In some patients the disease was localized in several other structures including the spleen liver eyes, lachrimal glands, cardiac muscle, and nervous system.

Laboratory examinations

Tuberculin tests

Forty four of the 61 patients gave a negative reaction to both the Pirquet and the Mantoux test ($\frac{1}{10}$ milligram of tuberculin) whereas 6 gave positive reactions to both these tests. In 11 cases the tests were contradictory that is in 10 cases the Pirquet test was negative, while the Mantoux test was positive, and in 1 case the reverse was observed. Thus the Pirquet test was negative in 54 out of 61 cases (about 90 per cent) In the 16 Mantoux positive cases, the sensitivity to tuberculin was never so marked that a reaction was obtained to a smaller dose than $\frac{1}{100}$ milligram of tuberculin.

TABLE III

THE RESULTS OF TUBERCULIN TESTS, PIRQUET AND MANTOUX ($\frac{1}{10}$ MILLIGRAM OF TUBERCULIN) OF 61 SARCOIDOSIS PATIENTS

	Males	*Females*	*Total*
Pirquet-negative, Mantoux negative	19	25	44
Pirquet-negative, Mantoux-positive	3	7	10
Pirquet-positive, Mantoux-negative	1	0	1
Pirquet-positive, Mantoux-positive	3	3	6
Total	26	35	61

left patella. They were brownish-red, comparatively firm, being raised above skin level. No desquamation or sign of destructive changes. General enlargement of the glands (some palpable glands up to the size of a date), spleen palpable. He had noticed the swelling of the glands 5–6 years ago, and the infiltrations in the skin 2 3 years ago. Somewhat short of breath during the last year

Histological examination of the lymphatic glands Masses of epithelioid cells were surrounded by a scanty connective tissue with lymphocyte infiltration. No necrosis. Here and there giant cells of the Langhans type. Nothing left of the original lymph node structure. Histological diagnosis Boeck's sarcoid."

Inoculation of guinea-pigs with gland tissue No response.

Radiological examination of the thorax Large hilus glands and enlarged paratracheal glands on the right side. Scattered parenchymal opacities in both lungs. A few cystic lesions in the bones of the hands. Pirquet, Mantoux ($\frac{1}{10}$ mg.) and Wassermann tests, all negative E.S.R. 8 mm. Normal findings on cytological examination of the blood. Kveim's reaction positive.

The patient was kept under observation for 3 years. The infiltrations of the skin gradually disappeared, but there was hardly any change in the lungs. The patient declared that his capacity for work was reduced.

Commentary The picture presented by infiltrations in the skin, glands, lungs, spleen and bones was characteristic of sarcoidosis. The patient was tuberculin-negative and Kveim-positive. A very potent antigen for Kveim's reaction was prepared from one of his glands.

In 17 cases there were manifestations of the disease in 3 of the above-mentioned 4 most important localizations. One of these patients deserves special attention as she presented a bony lesion in several fingers with swelling also of their soft structures in addition to a lupus-pernio-like rash on her face.

Case III Inga, H., schoolteacher's wife, aged 63 years, admitted to hospital for the first time in 1947 A slightly prominent, firmly elastic, bluish-red infiltration measuring 3 by 4 centimetres in the left cheek. Under vitro-pressure miliary foci. A bluish-red, spindle-shaped swelling of the second and fifth fingers of the *right hand*. No other finding on a physical examination. The finger lesions began 17 years ago, and the infiltration in the left cheek 4–5 years ago.

Radiological examination of the thorax ? Bilateral infiltration of the lungs. Pleural lesion. Cystic lesions in several phalanges of *her fingers*. *Pirquet* and *Mantoux* (1 mg.) negative. The diagnostic BCG reaction "*Doubtful early-reaction*. Kveim's reaction positive (tissue emulsions of brain and spleen negative) Treatment with calciferol, but after the daily administration of 150,000 units for weeks she developed severe and prolonged signs of poisoning with renal failure. She recovered completely after prolonged hospital treatment. She was periodically under medical supervision until 1949

Commentary The patient had lupus pernio-like sarcoidosis with involvement of the skin as well as of the lungs and bones of the fingers. A short course of calciferol provoked a prolonged and serious disease of the kidneys which ultimately healed.

One of the patients who died of sarcoidosis *some time after discharge* from hospital presented a multiple, finely nodular sarcoid rash chiefly on her limbs. Its appearance was somewhat unusual. She also suffered from great enlargement of the spleen and liver as well as from a heart disease which probably was also an expression of her extensive sarcoidosis.

Case IV Borghild, S Shop assistant, aged 28 years. Admitted to hospital in 1944 Emaciated, listless and breathless. Brownish-red, cutaneous-subcutaneous

As Table V shows, this cutaneous test proved positive in 54 out of 61 cases, that is in about 90 per cent. Among the 54 positive reactions 5 were "weak" whereas the papule provoked was very distinct in 49 cases. The reaction was negative in 7 cases These observations show that about 10 per cent of definite cases of sarcoidosis can be expected to give a negative Kveim reaction. It is probable that this cutaneous test when repeated, preferably with some other sarcoid antigen, would yield a positive reaction On the other hand, the results prove that the diagnostic significance of the test is not negligible.

Erythrocyte sedimentation rate

The erythrocyte sedimentation rate (Westergren) was estimated in 60 cases, in 20 of which the findings were within the normal limits. In 32 cases the erythrocyte sedimentation rate was between 20 millimetres and 50 millimetres, whereas in 8 cases it was over 50 millimetres. It will thus be seen that it is very often raised in sarcoidosis.

Haemoglobin

In 41 cases the haemoglobin figures were within normal limits.

The cytology of the blood was examined in 37 cases in 17 the monocyte counts* were under 5 per cent in 13 these counts were between 5 per cent and 10 per cent, and in 7 they were between 10 per cent and 20 per cent. Therefore we regard Boeck's observation concerning the monocyte count in his first patient (*see* p. 122) as indicating the exception rather than the rule. In none of our cases was marked eosinophilia or other cytological changes found

Serum-protein

Salvesen (1935) showed that the serum-protein might be increased in cases of sarcoidosis. Serum from 20 patients was therefore analysed, but in all cases the findings were within the normal range further there was no marked abnormality of the albumin globulin rates.

Serum-calcium

The calcium content of the serum was investigated in 21 cases in 6 the levels were elevated, ranging from 11 5 milligrams per cent to 13·4 milligrams per cent. In 15 cases the serum-calcium rate was within normal limits It will thus be seen that a moderate increase of serum-calcium is not uncommon in cases of sarcoidosis.

Signs and symptoms

The skin glands, lungs and bones are the most common sites of sarcoid invasion and perhaps also the most characteristic lesions occur in these places. In our 61 patients there were, however only 7 with simultaneous manifestations of the disease in all these four systems. The following is an account of sarcoidosis in its "classic" form.

Case II Eivind, L., a farmer aged 46 years, presented multiple nodules from the size of a pea to that of a hazel nut on his face, neck shoulders, upper arms and over the

* Authorities differ concerning the normal monocyte count One gives the figure as 5–10 per cent of the total circulating leucocytes, another 4–8 per cent, and a third 3–6 per cent but they seem to agree that monocytes are derived from the "reticulum" of the reticulo-endothelial system, a point which may be of some interest.—*Editor*

Case VI Odmund, P a forester aged 42 years, had a flat bluish-red infiltration about 1 centimetre in diameter on the tip of his nose. Physical examination showed nothing of interest except for slight enlargement of some of the superficial lymphatic glands. Duration of the disease 3 years.

Histological examination The infiltration on his nose showed "chronic inflammation Boeck's sarcoid probable.

Radiological examination Parenchymal opacities in both lungs. Bilateral hilar adenitis. Cystic clarification of the mid-phalanx of the right fourth finger

Guinea-pig inoculation This, and culture according to the sulphuric acid method of tissue excised from the nose, yielded no growth of tubercle bacilli.

Examination of the eyes Slight enlargement of both lachrymal glands, and traces of a healed iritis on the left side. Pirquet, Mantoux ($\frac{1}{10}$ mg) and Wassermann tests all negative. Kveim s test positive. Local Finsen treatment and several courses of arsenic were given. He was kept periodically under observation in the hospital for 11 years. The disease ran a benign course, and he was fully fit for work. The infiltration on the tip of his nose persisted but was less prominent.

Commentary This was a typical case of sarcoidosis with involvement of the skin, glands, lungs, bones, lachrymal glands and eyes. He was tuberculin-negative and Kveim-positive. Intracutaneous tests with an emulsion of normal cerebral tissue and normal splenic tissue yielded negative results. A histological examination of a Kveim papule showed under a uniform epidermis well-defined, nodular infiltrations composed of epithelioid cells and giant cells of the Langhans type with scanty lymphatic border and without necrosis. This condition is reminiscent of Boeck's sarcoid. Intracutaneous tests were also carried out with killed BCG ($\frac{1}{10}$ mg.) and killed tubercle bacilli (typhus humanus $\frac{1}{100}$ mg.). The resulting infiltrations were excised and examined histologically month later In both cases the histological report was "chronic specific inflammation. Epithelioid cell-tubercles A catgut thread in the skin did not provoke any characteristic tissue changes.

It will be seen that among the tissue emulsions only the one prepared from sarcoid tissue was capable of provoking a distinct reaction papule (Kveim's reaction). Killed tubercle bacilli were also capable of provoking tissue changes, but these were far from being so prominent as the "Kveim papule The histological tissue changes were more in conformity with those of classic tuberculosis whereas the sarcoid tissue emulsion provoked a tissue reaction whose histological picture was very similar to that of classic Boeck's sarcoid As will be pointed out later a similar tissue reaction provoked by killed tubercle bacilli can also be observed in healthy tuberculin-negative persons in whom the sarcoid tissue antigen does not, however provoke any reaction.

In Norway many cases of isolated pulmonary sarcoidosis have been discovered in the course of routine mass radiography of the lungs. The diagnosis may then be difficult, as shown in the following characteristic case.

Case VII Leif, F a forester aged 47 years, was admitted to hospital on January 4 1950, pulmonary changes having been discovered during a routine mass radiography As he was tuberculin-negative, he was admitted to this hospital for further examination. He felt ell, and the findings of a physical examination were negative

Radiological examination of the thorax *Bilateral*, symmetrical opacities of the lungs. Pleural involvement on the right side, presumably of a somewhat older date. His hands Osteitis cystoides multiplex. Pirquet and Mantoux (1 mg.) tests, negative Kveim reaction positive.

Commentary The diagnosis of sarcoidosis was based on the bilateral changes in the lungs, characteristic radiological change in the bones of his fingers, negative tuberculin tests and a positive Kveim test.

papules ranging from the size of a pea to that of a bean were present on the limbs and trunk, the lesions being less numerous on the latter area. Definite enlargement of liver and spleen Her illness had lasted about 3 years, and during the last year her general condition had deteriorated and she had become emaciated.

Radiological examination Bilateral pulmonary infiltration (Boeck's sarcoid? Tuberculosis?) No abnormality of the hands and feet.

Report of skin biopsy "Chronic, specific inflammation. Boeck's sarcoid probable. Pirquet and Mantoux (1 mg.) tests, negative. *Kveim's reaction positive. A systolic cardiac murmur was noted while she was in hospital, and she had repeated attacks of tachycardia Expert cardiological examination failed to identify the nature of her heart disease. Later she* was confined to bed at home, and died after 2 years from cardiac insufficiency with severe ascites.

Commentary This patient presented cutaneous lesions of sarcoidosis the malady affected also the lungs, liver spleen and perhaps the heart. She died 2 years later and a post mortem examination was not made

It may be very difficult to diagnose sarcoidosis if the patient suffers from a lupus-vulgaris like condition of the skin and gives positive reactions to tuberculin tests.

Case V Magnhild, E., a fisherman's wife, aged 48 Three years before admission to hospital for the first time (in 1947) she noticed a red "nodule" on the bridge of her nose It has grown since then. When she was 14 years old, an elder sister developed pulmonary tuberculosis, living at home till she died 2 years later On the bridge of the patient's nose there was a flat, brownish-red infiltration about 2 centimetres in diameter Yellowish foci in this infiltration were visible on vitro-pressure There was no enlargement of the glands, and a physical examination proved in other respects negative

Radiological examination of the thorax, hands and feet showed no abnormalities. Pirquet and Mantoux ($\frac{1}{10}$ mg.) positive. Diagnostic BCG reaction "Positive early reaction." Kveim's reaction positive (weak)

Histological examination of the infiltration on her nose Boeck's sarcoid most probable" Biopsy of suspect papules in the nasal mucosa gave the same result. Guinea pig inoculation of tissue from the infiltration on her nose and culture tests failed to give evidence of tuberculosis. From 1947 to 1952 she was admitted to hospital *on six occasions. The infiltration on her nose has spread* somewhat outwards and has constantly become larger after temporary improvement during and after hospital *treatment. No change in her lungs. General condition good.*

Commentary In this case the differential diagnosis with regard to lupus vulgaris was very difficult as the manifestations of her disease were confined to the skin. It is generally agreed that, from the clinical point of view the infiltrations of lupus vulgaris can resemble those of sarcoidosis in every respect. In this case the histological examination gave support to the diagnosis, but this support must be characterized as very qualified or conditional Her tuberculin reactions were positive, and this is seldom the case with sarcoidosis (*see* Table III) The negative results of inoculation of guinea-pigs with the patient's tissues and of culture on egg media, are an important argument *against lupus vulgaris.* Also Kveim's reaction was positive.

In many of our cases several cutaneous tests were carried out with emulsions of sarcoid tissue and other tissues, as *well as with BCG and killed tubercle* bacilli The history of one of these patients will now be given as these tests will be discussed and closely scrutinized with reference to their diagnostic value and their ability to throw light on the aetiology of sarcoidosis.

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Commentary This was a typical case of sarcoidosis with involvement of the skin, glands, lungs, bones, lachrymal glands and eyes. He was tuberculin-negative and Kveim-positive. Intracutaneous tests with an emulsion of normal cerebral tissue and normal splenic tissue yielded negative results. A histological examination of a "Kveim papule showed under a uniform epidermis well-defined, nodular infiltrations composed of epithelioid cells and giant cells of the Langhans type with scanty lymphatic border and without necrosis This condition is reminiscent of Boeck s sarcoid." Intracutaneous tests were also carried out with killed BCG ($\frac{1}{10}$ mg.) and killed tubercle bacilli (*typus humanus* $\frac{1}{100}$ mg.) The resulting infiltrations were excised and examined histologically a month later In both cases the histological report was "chronic specific inflammation. Epithelioid cell-tubercles A catgut thread in the skin did not provoke any characteristic tissue changes.

It will be seen that among the tissue emulsions only the one prepared from sarcoid tissue was capable of provoking a distinct reaction papule (Kveim s reaction) Killed tubercle bacilli were also capable of provoking tissue changes, but these were far from being so prominent as the "Kveim papule The histological tissue changes were more in conformity with those of classic tuberculosis whereas the sarcoid tissue emulsion provoked a tissue reaction whose histological picture was very similar to that of classic Boeck s sarcoid As will be pointed out later a similar tissue reaction provoked by killed tubercle bacilli can also be observed in healthy tuberculin-negative persons in whom the sarcoid tissue antigen does not, however provoke any reaction.

In Norway many cases of isolated pulmonary sarcoidosis have been discovered in the course of routine mass radiography of the lungs. The diagnosis may then be difficult, as shown in the following characteristic case.

Case VII Leif F forester aged 47 years, was admitted to hospital on January 4 1950, pulmonary changes having been discovered during a routine mass radiography As he was tuberculin-negative, he was admitted to this hospital for further examination. He felt well, and the findings of a physical examination were negative.

Radiological examination of the thorax Bilateral, symmetrical opacities of the lungs. Pleural involvement on the right side, presumably of a somewhat older date. His hands Ostitis cystoides multiplex. Pirquet and Mantoux (1 mg.) tests, negative K eim reaction positive.

Commentary The diagnosis of sarcoidosis was based on the bilateral changes in the lungs, characteristic radiological change in the bones of his fingers, negative tuberculin tests and positive Kveim test.

One of the other patients in this group had been vaccinated with BCG and had become tuberculin-positive before a pulmonary form of sarcoidosis was discovered.

Case VIII Ingvald, F., a shop assistant, aged 35 years. Admitted to hospital in 1950 He had been vaccinated with BCG in 1943 and since then had been tuberculin-positive During the previous 3 years *he had often been troubled by coughing, and had* felt tired, but had continued to work full time.

Examination in hospital showed his general condition to be good and nothing abnormal *was found apart from some bronchitic sounds over the lungs*

Radiological examination Bilateral miliary-like opacities of the lungs. Negative *findings* in hands and feet No tubercle bacilli found in the sputum (on direct examination and culture) *Pirquet and Mantoux ($\frac{1}{10}$ mg.) tests positive Diagnostic BCG* reaction Negative early reaction" Kveim reaction positive, E.S.R 4 millimetres.

A Kveim papule" and a late papule following a BCG reaction were examined *histologically both showing chronic specific inflammation with a "Boeck-like" picture.*

Six months later a radiological examination showed that the lesions in the lungs were resolving.

Commentary A man who had become tuberculin-positive after BCG vaccination developed a pulmonary lesion 3–4 years later The radiological picture was that of sarcoidosis. Tuberculin tests continued to be positive, but the diagnostic BCG test *showed a negative early reaction" Tubercle bacilli could not be found in the sputum.* Kveim's reaction was positive and the late papules following it and BCG inoculation showed chronic inflammation" The disease of his lungs has run a *benign course*

Of late years the part played by foreign body granulomas in provoking sarcoidosis has attracted considerable attention. Several observations seem *to show* that the sarcoidosis patient has an increasing tendency to react to trauma by developing foreign body granulomas. Such cases have also been observed in the present series.

Case IX Cato O., an engine-driver aged 29 years, fell when 3 years old, breaking a bottle and cutting his right forearm. After 26 years he noticed a remarkable discoloration of his skin which was most marked in the border zone of the old wound. In 1948, a "ball" developed in his forehead at a point where for many years he had had a scar resulting from "butting" when playing football This infiltration was removed by operation histological examination showed a "foreign-body granuloma with the Boeck picture" Six months later he developed a brownish discoloration in the scar of the first operation. Biopsy of this lesion gave the same finding as on *the first occasion* The patient was now admitted to hospital

February 1949 On his forehead, just below the hair limit, was a horizontal operation scar 4 centimetres in length. Above and below it was a palpable *oblong infiltration* with discoloration of the skin There were palpable glands in the neck, inguinal region and axillae On the volar aspect of his right forearm was a large scar from a burn.

Radiological examination Bilateral infiltration of the lungs and hilar adenitis. Negative findings in hands and feet

Pirquet and Mantoux (1 mg.) tests negative Diagnostic BCG reaction "Negative early reaction" *Kveim reaction positive*

May 1949 The infiltration in the operation scar on his forehead more prominent also brownish-red infiltrations detected in the border of the scar on his right forearm. *There were signs of a chronic iridocyclitis* He complained of marked dryness of his mouth.

August 1949 The infiltrations in his forehead and in the scar on his right forearm have increased. The hospital's specialist in plastic surgery removed the infiltration in and about the scar on the forehead. The report on the histological examination of the tissues removed was the same as on the previous occasion. Inoculation of the tissues, into guinea-pigs and cultures for tubercle bacilli gave negative results. During his stay in hospital the patient developed numerous brown papules, as large as a grain of corn on the leg below the knee (Boeck s sarcoid on histological examination).

March 1951 General condition good. No recurrence in the scar on his forehead. Scattered brownish infiltrations, as large as a grain of corn, still on his legs and forearms. Radiological examination showed extension of the bilateral pulmonary lesion.

During his stay in hospital, examination of a Kveim-papule showed granulation tissue of the type associated with Boeck s sarcoid (tissue emulsions of normal spleen and of brain gave no reaction).

A late reaction followed BCG inoculation, the papule provoked being excised after 3 months. Histological examination showed granulation tissue of the Boeck sarcoid type. Infiltrations which had developed spontaneously in the skin of his arm and leg showed the histological structure of Boeck s sarcoid.

Commentary A man, aged 29 years, developed (in a scar beginning in childhood after butting" football injury) an infiltration presenting the clinical features of Boeck's sarcoid. Histological examination showed a foreign-body granuloma" On further examination other manifestations of sarcoidosis justified the diagnosis of this disease, for the lungs, eyes and salivary glands were involved. While under observation, the patient developed new sarcoid infiltrations scattered in the skin and in the scar of a wound caused by broken glass. A vaccination scar was also the seat of such infiltration. Injections of emulsions of sarcoid tissue and BCG inoculation provoked infiltrations the clinical and histological ppearances of which coincided with those of nodules which had developed spontaneously Injections into the skin of other tissue emulsions did not have the same effect. Negative results have hitherto been obtained with injections of calcium salts into the skin. It would seem that in this case the sarcoidosis had favoured the development of foreign-body granulomas.

In our sarcoidosis material the disease has been observed in many areas other than those mentioned above These comparatively rare localizations among our patients have, however played a subordinate part in the clinical picture. The literature of the subject contains several important surveys of these special localizations. Thus *Colover (1948)* has given a detailed description of sarcoidosis of the nervous system Wille (1946) has described sarcoidosis of the mucous membranes, and Longcope and Freeman (1952) have dealt in great detail with involvement of the eyes.

Bilateral h lar adenitis and erythema nodosum in tuberculin-negative patients have attracted much attention, particularly among Scandinavian workers—Abramson (1943), Ustvedt (1939), Löfgren (1943 and 1946), Vogt (1930 and 1946), Kahrs (1947) and others. In a few cases this symptom-complex must be taken to indicate sarcoidosis, the prognosis for the latter is comparatively good. Ustvedt (1939) has emphasized that bilateral hilar adenitis seems to occupy an important place in sarcoidosis, and has suggested that the frequency with which the disease is located in this position may give us a clue to an unknown infecting agent which perhaps, causes the disease, and possibly uses the respiratory tract as its portal of entry

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Examination in hospital showed his general condition to be good, and nothing abnormal was found apart from some bronchitic sounds over the lungs.

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BACTERIOLOGICAL INVESTIGATIONS. ANIMAL INOCULATIONS

Examinations of sections of sarcoid tissue have occasionally yielded positive findings of acid-fast rods,—Kyrle (1921), Dittrich (1931), Schaumann and Hallberg (1941),—but in none of these cases has tubercle bacilli been isolated by direct culture or by animal inoculations. In the cases in which tubercle bacilli have been isolated by culture or inoculation of "sarcoidosis" material there is also the possibility that this diagnosis was not correct, for it is often very difficult to distinguish between lupus vulgaris and cutaneous sarcoidosis, special methods of examination being needed in certain cases.

At my hospital, many attempts have been made to isolate tubercle bacilli from sarcoid tissue by the technique employed to isolate tubercle bacilli from lupus vulgaris tissue. By direct culture for tubercle bacilli from lupus tissue by the sulphuric acid method, and by inoculation of guinea-pigs (36 cases of lupus vulgaris), Danbolt and Brandt (1939) have succeeded in isolating tubercle bacilli in every case. In a case of sarcoid-like skin tuberculosis, Danbolt and Brandt (1938) succeeded in isolating a strain of tubercle bacilli of the avian type. In our attempts to isolate tubercle bacilli from sarcoidous tissue, we have undertaken direct culture of tissues on egg media, and we have also inoculated fowls, guinea-pigs and rabbits with such tissue. Kveim (communication not published) undertook in 1940 such an examination of 20 selected cases of sarcoidosis from my hospital, but his results were invariably negative. Employing the same technique, Danbolt and Brandt (1939) examined 6 further cases of sarcoidosis, again with negative results. In their survey of the literature of similar investigations, Longcope and Freiman (1952) quote a statement by Pinner which concluded with the following words: "the number of positive results is very small, the number of completely convincing positive results is insignificant". We therefore conclude that when tubercle bacilli can be cultured from lesions suspected of being "sarcoid" the lesions must be regarded as tuberculous however suggestive of sarcoidosis the clinical picture may be. Jaques (1952) is also of this opinion, and further has stated that "the presence of caseation necrosis should negate the diagnosis of sarcoidosis."

There is one objection—much debated—to this point of view. It concerns the significance of the "positive anergy" which may exist and which may provoke so great a weakening or devitalization of any tubercle bacilli present in sarcoid lesions that these bacilli are no longer capable of growing on artificial media or provoking tuberculosis in experimental animals. With this reservation we must, however, insist that comprehensive and carefully executed attempts to isolate tubercle bacilli from sarcoid tissue have failed so systematically in cases of sarcoidosis that the few and often uncertain findings of these bacilli do not carry much weight.

Löfgren and Lundbäck (1950) claim to have isolated a virus from 6 cases of sarcoidosis (2 cases of chronic sarcoidosis and 2 with the syndrome of bilateral hilar adenitis, negative or weak tuberculin reactions and erythema nodosum). The virus belonged to the "influenza-mumps-Newcastle disease group". Further investigations are necessary before we can be sure of the validity of this work.

HISTOLOGICAL INVESTIGATIONS

As early as 1897 Boeck maintained that the histological picture in his first case was of a special character distinct from that of ordinary tuberculosis of the skin He found the histological changes of sarcoidosis so characteristic that on several occasions he is said to have exclaimed A glance down the microscope is enough for the diagnosis!" Later experience, however has shown that the matter is not so simple as all that In some cases, to be sure, the histological picture may be so obvious that on the basis of it alone an experienced pathologist can claim that there is overwhelming evidence for diagnosing sarcoidosis. But very often, even when the clinical evidence of sarcoidosis is certain a histological section may show granulation tissue indistinguishable from that of lupus vulgaris. On the other hand, as Freudenthal (1948) has maintained a serial section of lupus vulgaris infiltrations may often show areas of granulation tissue indistinguishable histologically from those of typical sarcoid

Longcope and Freiman (1952) have given a detailed account, with exact references to the literature, of the research in recent years into the histology of sarcoidosis, and they have supplemented this work by a series of excellent illustrations. Their survey shows that certain features are quite characteristic of the tissue changes of sarcoidosis which give sound reason for emphasizing the importance of biopsy as an essential requirement for diagnosis.

Another important work on the histology and aetiology of sarcoidosis was published by Jaques (1952) His excellent description of the histology of sarcoidosis ran as follows

> Histologic appearance Superficially the histologic features of sarcoidosis resemble those seen in tuberculosis, but there are subtle differences The absence of caseation necrosis is stressed by most observers, although occasionally a report does mention caseation necrosis occurring in sarcoidosis. On the other hand, fibrinoid necrosis frequently is encountered in the centre of the granulomas of sarcoidosis Silver impregnation reveals a delicate reticulum in the sarcoid lesions which, however generally is present also in tuberculosis in the absence of caseation Some authors stress the observation that in tuberculosis the giant cells are larger and have more nuclei than those in sarcoidosis Rakov and Taylor noted that in sarcoidosis the epithelioid cells usually are larger and more cuboidal and that individual lesions do not conglomerate as they do in tuberculosis. Since superficially a similar histologic picture can be produced by a number of different agents, such as leprosy syphilis, typhoid lymphogranuloma venereum, brucellosis, torulosis, *Schistosoma mansoni* infestation, and foreign bodies, no definite conclusions regarding the cause of sarcoidosis can be drawn from the histologic appearance alone.

All the histological examinations of my hospital s quite large material of cases of sarcoidosis, skin tuberculosis and other chronic lesions of the skin are carried out at the University Institute for Pathology under Professor Kreyberg He has for a long time held views on the histology of sarcoidosis which are in conformity with those of Jaques The histological examination of suspect tissues can yield valuable evidence in support of the clinical diagnosis, but cannot by itself form the basis for the diagnosis. Nor can the histological findings in sarcoidosis, as known today give us definite clues to the aetiology of this disease. For as has just been pointed out, similar histological tissue reactions can be provoked by several different agents.

subject. Detailed bibliographies concerned with these problems are also to be found in the monographs already mentioned. Björnstad found that about two-thirds of his 71 sarcoidosis patients were tuberculin-negative (giving no reaction to doses of tuberculin up to 1 milligram). It will be seen from Table VI that 12 (or 17 per cent) reacted to up to $\frac{1}{10}$ milligram of tuberculin, and that only 2 (2·8 per cent) reacted up to $\frac{1}{100}$ milligram of tuberculin, whereas there was not a single patient in whom tuberculin sensitivity was so marked that a reaction followed doses of tuberculin of less than $\frac{1}{100}$ milligram.

TABLE VI

Tuberculin Reactions (Bjornstad)

	Tuberculin doses		*Number of patients*	
Positive	$\frac{1}{1000}$ mg.	+	0	21 (29·6 per cent)
	$\frac{1}{100}$		2	
	$\frac{1}{10}$	+	10	
	1	+	8	
	10	+	1	
Negative	$\frac{1}{10}$ mg.		14	50 (70·4 per cent)
	1		27	
	10	+	9	

Bjornstad has also investigated the tuberculin sensitivity of his patients in relation to their age. He found that even after the age of 40 years, two-thirds were tuberculin-negative (Mantoux test, using 1 milligram of tuberculin). For comparison it may be pointed out that Norwegian statistics concerned with tuberculin sensitivity in a great number of healthy adults over the age of 40 years have shown that 90–100 per cent were tuberculin-positive (Ustvedt, 1938).

In doubtful cases, a tuberculin sensitivity which is slight or has died *out* will give good support to the diagnosis of sarcoidosis. On the other hand, a positive reaction up to $\frac{1}{100}$ milligram of tuberculin cannot exclude the diagnosis of sarcoidosis It should be added that in none of our cases was the disease complicated by a tuberculosis capable of changing a reaction which had earlier been negative to tuberculin.

Several theories have been advanced to explain the weakness or absence of tuberculin sensitivity in sarcoidosis. The argument that this state of affairs is due to these patients not having been exposed to infection with tuberculosis in the same way as the average human being, is not valid, for many cases have been recorded in which the reaction to tuberculin was positive before the patient developed sarcoidosis, becoming negative when he developed this disease. So-called "tuberculin-revertors" are, however also to be observed in other maladies. Yet we can hardly doubt that tuberculin anergy in cases of sarcoidosis must be interpreted as characteristic of this disease, and that certain processes connected with it interfere with the capacity of the individual to react to tuberculin. Lemming (1940) has pointed out that tuberculin-positivity cannot be provoked in sarcoidosis patients in spite of repeated inoculations with BCG In the course of mass vaccinations with BCG it is, however not rare to find such resistant

BLOOD INVESTIGATIONS SEROLOGICAL INVESTIGATIONS

In their monograph on sarcoidosis, Longcope and Freiman (1952) have given an exhaustive survey of the investigations undertaken in connexion with cytological changes in the blood the serum proteins, the calcium and phosphorus content of the serum, and other laboratory tests. Boeck s finding of an increased number of monocytes in his first patient has often been made by subsequent workers in other cases. Salvesen s demonstration (1935) of raised serum protein levels is of interest. Hyperglobulinaemia and hypercalcaemia has often been found and this may possibly help to explain why treatment with calciferol very often provokes signs of poisoning in sarcoidosis patients. Our findings in regard to these matters have been stated

In spite of these and other comprehensive investigations, we must admit that no specific changes in the cytology or chemistry of the blood have as yet been demonstrated.

The new serological methods for the demonstration of a tuberculous infection (*see* Middlebrook and Dubos, 1948) have also been applied to the solution of the problem of sarcoidosis and the possibility of its being of tuberculous origin. The principle underlying the Middlebrook serological reaction is the observation that washed sheep s blood corpuscles can be sensitized by a polysaccharide extract of tubercle bacilli or by old tuberculin with the result that the sheep s blood corpuscles are agglutinated when the serum of tuberculous patients is added to them. The reaction is usually regarded as positive when agglutination occurs in a serum dilution of 1 8 or more. This reaction has been found to be positive in from 50 per cent to 80 per cent of the sera taken from tuberculous persons, but it has also been positive in from 5 per cent to 17 per cent of healthy persons. This serological reaction has not therefore been of any practical value for the diagnosis of tuberculosis.

Several investigators have applied Middlebrook s reaction also to sarcoidosis. Ulstrup (1951) found it positive in 16 out of 19 sarcoidosis patients, and Smith and Scott (1950) in 7 out of 11 such patients. In my hospital Ødegaard (1953) has undertaken a certain number of such investigations, and among 86 patients suffering from diseases unrelated to tuberculosis he found the reaction positive in 10 and negative in 76 The reaction was positive in 13 out of 19 cases of pulmonary tuberculosis, being negative in 6 Among 20 cases of lupus vulgaris, the reaction was positive in 13 and negative in 7 In 20 cases of sarcoidosis there were 5 with a positive and 14 with a negative Middlebrook reaction This new serological test has, as already pointed out in the case of tuberculosis, yielded so many non-specific reactions that it has small diagnostic value. The behaviour of this test in cases of sarcoidosis can hardly be used as an argument in favour of a tuberculous aetiology in this disease.

SKIN TESTS IN SARCOIDOSIS

Tuberculin skin tests

It is a remarkable fact, known for a long time, that most sarcoidosis patients show a tuberculin-sensitivity which is weak or has died out. Björnstad (1948) has published a study based on 71 definite cases in all of whom there were skin manifestations of this disease His study included a survey of the literature of the

investigations were repeated at my hospital and published by Björnstad (1948) who was able to show that sarcoid-like histological changes can also be provoked by the intracutaneous injection of killed tubercle bacilli into healthy tuberculin-negative persons. He came to the conclusion that this histological test cannot be regarded as specific for sarcoidosis.

It is still an open question whether an injection of killed tubercle bacilli into sarcoidosis patients provokes a histological reaction differing from that observed in other persons with a weak or absent tuberculin sensitivity. Only more comprehensive investigations can answer this question.

Lemming's demonstration (1942) of sarcoid-like infiltration in the skin of a sarcoidosis patient after BCG inoculation has prompted more comprehensive investigations of cutaneous reactions to BCG in such cases. Leider and Hyman (1950) maintain that sarcoid patients seem to react in a special way to BCG inoculation. While healthy tuberculin-negative persons develop a cutaneous reaction which in its further course corresponds to phase I of Koch's Fundamental Experiment, and healthy tuberculin-positive persons develop a reaction corresponding to phase II of the same test, sarcoid patients present a cutaneous reaction the clinical course of which is different, a slowly growing papule with the appearance of a sarcoid nodule developing in 5–7 days. Leider and Hyman maintain that "This is a newly described experimental reaction to the tubercle bacillus. It was first noted by Lemming, then confirmed by Warfvinge, Björnstad and Danbolt. It is again confirmed here."

Ustvedt and Aanonsen (1949) have devised a diagnostic BCG test which is of special interest in this field. The test consists of pricking the skin through a drop of fresh BCG vaccine containing 20 milligrams of BCG per millilitre. Persons who have been infected with tubercle bacilli develop a brownish-red papule which, starting after 2–3 days and increasing up to the eighth day, is an expression of phase II of Koch's Fundamental Experiment. These observers have called this reaction a "positive early reaction". If this papular reaction has not developed in the course of 8 days, they apply the term negative early reaction to it. If a positive early reaction does not develop, a papule of the type often appearing on BCG vaccination of tuberculin-negative persons develops from 8 to 14 days after the inoculation. The same observers interpret a positive early reaction as the expression of a specific allergy even if the person concerned is tuberculin-negative. Danbolt (1948) has applied this diagnostic BCG test to 19 sarcoid patients. Among 15 Pirquet-negative sarcoid patients were 9 giving a positive Mantoux reaction to 1 milligram of tuberculin. Of these 9 there were 6 who gave a negative early reaction. These findings may mean that the positive Mantoux reaction must be assumed to be non-specific. Phase I of Koch's Fundamental Experiment is demonstrable on BCG inoculation in most cases of sarcoidosis, and this would be remarkable if sarcoidosis is a tuberculous disease (*see also* Table IV).

The observations hitherto made in my hospital with regard to cutaneous reactions after the BCG inoculation of sarcoidosis patients do not seem to indicate that these patients react differently by and large from healthy tuberculin-negative persons as suggested by Leider and Sulzberger (1949). Intracutaneous BCG vaccination of tuberculin-negative school-children often gives rise to late papules, and it would be most interesting to examine them histologically. In our 61 cases, 11 late papules following BCG inoculation of sarcoidosis patients have been examined

individuals (without sarcoidosis). This state of affairs has been discussed by Ustvedt (1951) and others.

Jadassohn regarded sarcoidosis as a tuberculous disease, and he advanced his well-known theory concerning "positive specific anergy" which he presented to explain the absent or weak tuberculin sensitivity of these patients. The cause of this anergy was taken to be a specific change in the capacity of the body to react to tuberculin—an expression, as Leider and Sulzberger (1949) would have it, of "an allergic transformation" In other words, this type of anergy is quite different from the anergy due to the individual never having come into contact with tuberculosis or from the anergy existing when a previously tuberculin-sensitive person temporarily becomes anergic because of some other disease such as measles or meningitis Several investigations have been undertaken to demonstrate possible "anticutins"—substances capable of weakening a tuberculin reaction and circulating in the blood of sarcoidosis patients. The results of these investigations have been contradictory—Martenstein and Jadassohn (1923) Kissmeyer and Schultz (1931) Wells and Wylie (1949) and others

Pyke and Scadding (1952) have recently published an observation of great theoretical interest. It was noticed that, under cortisone treatment, tuberculin-negative sarcoid patients showed a change of tuberculin sensitivity with the result that they became Mantoux positive. These observers do not attempt to give any explanation of this phenomenon, but they point out that it "indicates something peculiar about the negative Mantoux reaction in sarcoidosis

In the discussion of tuberculin and other skin tests, little attention has been paid to the local conditions of absorption by the skin. Seeberg (1947) has, however shown that a whole series of non specific factors can change the conditions under which absorption proceeds in the skin, and can thus weaken the appearance of allergic reactions in the skin A sun-erythema for example, can have this effect, and the same observation can be made during menstruation—(Seeberg, 1950, and Hård 1950) Our knowledge of the phenomena of absorption by the skin, particularly in cases of sarcoidosis, is still very limited Investigations in this field may possibly also help to throw light on the curious "anergy" so often to be found in sarcoidosis patients

Skin reactions provoked by inoculations of tubercle bacilli (killed or alive, virulent or attenuated—BCG)

Lemming (1940) and Warfvinge (1943 1945) were the first to seek to explain the defective tuberculin sensitivity of sarcoidosis patients by employing suspensions of tubercle bacilli, either BCG (Lemming) or virulent or killed tubercle bacilli (Warfvinge) The latter using virulent tubercle bacilli inoculated the skin of a woman suffering simultaneously from sarcoidosis and pulmonary tuberculosis. A nodule which developed in her skin was excised after 4 weeks. It showed the characteristic histological structure of sarcoidosis and tubercle bacilli could not be found in sections of it. These investigations were extended to include the employment of killed tubercle bacilli By this procedure a cutaneous reaction could be provoked in sarcoidosis patients, and when a histological examination was made after 4–6 weeks, the granulation tissue presented the usual picture of sarcoidosis. Warfvinge (1945) published his work under the title "Une réaction cutanée en lymphogranulomatose bénigne, produit par des bacilles mortes de Koch." Similar

investigations were repeated at my hospital and published by Björnstad (1948) who was able to show that sarcoid-like histological changes can also be provoked by the intracutaneous injection of killed tubercle bacilli into healthy tuberculin-negative persons. He came to the conclusion that this histological test cannot be regarded as specific for sarcoidosis.

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The observations hitherto made in my hospital with regard to cutaneous reactions after the BCG inoculation of sarcoidosis patients do not seem to indicate that these patients react differently by and large from healthy tuberculin-negative persons as suggested by Leider and Sulzberger (1949). Intracutaneous BCG vaccination of tuberculin-negative school-children often gives rise to late papules, and it would be most interesting to examine them histologically. In our 61 cases, 11 late papules following BCG inoculation of sarcoidosis patients have been examined

individuals (without sarcoidosis) This state of affairs has been discussed by Ustvedt (1951) and others.

Jadassohn regarded sarcoidosis as a tuberculous disease, and he advanced his well known theory concerning "positive specific anergy" which he presented to explain the absent or weak tuberculin sensitivity of these patients. The cause of this anergy was taken to be a specific change in the capacity of the body to react to tuberculin—an expression as Leider and Sulzberger (1949) would have it, of "an allergic transformation" In other words, this type of anergy is quite different from the anergy due to the individual never having come into contact with tuberculosis or from the anergy existing when a previously tuberculin-sensitive person temporarily becomes anergic because of some other disease such as measles or meningitis. Several investigations have been undertaken to demonstrate possible "anticutins"—substances capable of weakening a tuberculin reaction and circulating in the blood of sarcoidosis patients The results of these investigations have been contradictory—Martenstein and Jadassohn (1923) Kissmeyer and Schultz (1931) Wells and Wylie (1949) and others.

Pyke and Scadding (1952) have recently published an observation of great theoretical interest It was noticed that under cortisone treatment tuberculin-negative sarcoid patients showed a change of tuberculin sensitivity with the result that they became Mantoux positive. These observers do not attempt to give any explanation of this phenomenon, but they point out that it "indicates something peculiar about the negative Mantoux reaction in sarcoidosis"

In the discussion of tuberculin and other skin tests, little attention has been paid to the local conditions of absorption by the skin Seeberg (1947) has, however shown that a whole series of non specific factors can change the conditions under which absorption proceeds in the skin, and can thus weaken the appearance of allergic reactions in the skin A sun-erythema for example, can have this effect and the same observation can be made during menstruation—(Seeberg, 1950 and Hård 1950) Our knowledge of the phenomena of absorption by the skin, particularly in cases of sarcoidosis, is still very limited Investigations in this field may possibly also help to throw light on the curious "anergy" so often to be found in sarcoidosis patients.

Skin reactions provoked by inoculations of tubercle bacilli (killed or alive virulent or attenuated—BCG)

Lemming (1940) and Warfvinge (1943 1945) were the first to seek to explain the defective tuberculin sensitivity of sarcoidosis patients by employing suspensions of tubercle bacilli either BCG (Lemming) or virulent or killed tubercle bacilli (Warfvinge) The latter using virulent tubercle bacilli inoculated the skin of a woman suffering simultaneously from sarcoidosis and pulmonary tuberculosis. A nodule which developed in her skin was excised after 4 weeks It showed the characteristic histological structure of sarcoidosis and tubercle bacilli could not be found in sections of it. These investigations were extended to include the employment of killed tubercle bacilli By this procedure a cutaneous reaction could be provoked in sarcoidosis patients, and when a histological examination was made after 4–6 weeks, the granulation tissue presented the usual picture of sarcoidosis. Warfvinge (1945) published his work under the title "Une réaction cutanée en lymphogranulomatose bénigne, produit par des bacilles mortes de Koch" Similar

fractions examined hitherto also gave unspecific reactions). It is a remarkable fact that the antigenic principle does not seem to be destroyed by boiling. This was first observed by Putkonen, and confirmed by Lomholt and by us. However such boiled antigens seem to have a reduced potency

Intracutaneous injection of this antigen, in a dose of 0 10 to 0·20 only caused a temporary reaction due to mechanical causes in normal individuals But in patients with Boeck s sarcoid there developed after a few days or in the course of the first two weeks, rarely even later a brownish-red papule which has a peculiar torpid course of development. It usually persisted for several months, with enlargement during the first few months. Spontaneous recession then set in, and in most cases the papule disappeared by the end of a year, in some cases leaving small, pigmented scar The reaction papules are usually about 5 millimetres in diameter In rare cases they may be larger even up to 17 millimetres. Clinically they resemble spontaneous sarcoid nodules and the histological similarity may also be striking. But in contrast to the spontaneous nodules, these reaction papules recede spontaneously

Since 1942, 24 different suspensions of sarcoid tissue have been prepared for Kveim s reaction at my hospital. Most have been prepared from "sarcoid" lymphatic glands, but even lymphatic tissue suspensions show variations in their ability to provoke reaction papules. It is therefore necessary clinically to test every newly prepared "antigen" before using it for the purpose of diagnosis.

Kveim s reaction is regarded as positive when an intradermal injection of the antigen is followed by a papule which is evident a month later and persists for one or several months. It is therefore essential if our evaluation of this skin test is to be correct, for the patient to be kept under observation for at least a month or two but preferably for several months. The usefulness of this test is therefore somewhat limited. However sarcoidosis runs a chronic course, and its diagnosis often requires a long period of observation (see Figs. 22–25).

Danbolt (1951) has published the results of an investigation of the outcome of Kveim s reaction. Among 76 persons, some healthy and others suffering from disease other than sarcoidosis were 5 patients in whom Kveim s reaction was positive, that is it was non-specific in 6 5 per cent. On the other hand, among 46 clinically definite cases of sarcoidosis there were 41 with a positive Kveim reaction and 5 were Kveim-negative thus about 90 per cent of the sarcoidosis patients were Kveim-positive (*see also* Table V) (Fig. 26).

A histological examination of a reaction papule of the Kveim reaction type usually shows a structure closely resembling that of a sarcoid nodule which has arisen spontaneously A tuberculoid tissue structure" *can, however* be provoked by a great variety of poisons and is therefore not specific for the "sarcoid tissue antigen

Skin reactions provoked by tissue suspensions other than sarcoid tissue

Since it was shown that heat-sterilized sarcoid tissue suspension can provoke indolent papules clinically and histologically very like sarcoid nodules which have developed spontaneously reports have been received from different quarters concerning the action of other tissue suspensions on sarcoid patients. Even in his preliminary communications, Kveim stated that he had not been able to provoke similar reaction papules with a heat-sterilized suspension of pus from lymphogranuloma venereum (Frei's antigen). These investigations have been continued at my hospital with heat-sterilized suspensions of glands from Hodgkin s disease,

histologically In a few cases the histological structure closely resembled that of typical sarcoidosis, and in other cases the tissue changes had the appearance of classic tuberculosis Further investigations in this field are most desirable. Our own investigations do not seem to argue in favour of employing BCG inoculation as a diagnostic skin test for sarcoidosis.

Skin reactions provoked by heat-sterilized suspensions of sarcoid tissue (Kveim s reaction)

Williams and Nickerson in 1935 reported that heat sterilized suspensions of sarcoid tissue are capable of provoking a cutaneous reaction in sarcoid patients. Their report roused little interest in the United States of America, and it was published in a journal not available in Norway Independent observations, not based on the work of Williams and Nickerson, were carried out in my hospital and in 1941 Kveim published a preliminary communication on "A new and specific cutaneous reaction in Boeck s sarcoid." The investigation of this skin test (Kveim s reactions) were continued at my hospital by Danbolt (1943 1951) Danbolt and Wisløff Nilsen (1945) and elsewhere in Scandinavia by Putkonen (1943), Lomholt (1943) and Haxthausen (1948), and in the United States of America by Nelson (1948) Leider (1948) and several others. In their large monograph, Longcope and Freiman (1952) have given a survey of the significance of Kveim s reaction in sarcoidosis, and they add It seems probable, however that an open mind and new methods of approach such as are suggested by the Kveim reaction, for example, may eventually prove more profitable than endless wrangling over the role of the tubercle bacillus in the etiology of sarcoidosis."

The antigen for Kveim s reaction is prepared in the following way (Danbolt 1951)

The antigen used is prepared from sarcoid tissue The best antigens are prepared from enlarged lymph glands, infiltrated with the granulation tissue typical of the disease Usable antigens may also be prepared from cutaneous sarcoid nodules. We have also prepared workable antigens of extirpated distal finger joints with destructive osteitis cystoides with penetration of sarcoid tissue of the skin Antigens prepared from affected tonsils usually give unspecific reactions, undoubtedly because of bacterial toxins.

The sarcoid tissue to be used in the preparation of antigen is examined histologically and inoculated in guinea-pigs in order to make sure that there are no tubercle bacilli in the tissue. The sarcoid tissue to be used is weighed and then cut up with scissors and pincette as fine as possible The tissue mass is then ground to a paste in a mortar physiological saline solution is added 1 10 The suspension is then filtered through several layers of gauze to remove larger particles of tissue and the mixture is heated in a water bath to 60° C for 2 hours. This is repeated the following day and ordinary sterility controls are made If these are in order the suspension is diluted with an equal amount of physiological saline with the addition of 0 5 per cent phenol The prepared antigen will then be a heat sterilized tissue suspension in the proportion 1 20 with 0·25 per cent phenol.

Our experiments have shown that the active principle in the antigen follows the corpuscular elements and is not soluble in water A Berkefeld filtrate of this suspension was ineffective while a new suspension of the filtered out tissue elements was active The active principle is not soluble in ether Attempts to prepare satisfactory antigens from precipitated albumin fractions has as yet not yielded positive results (the albumin

from normal spleen and brain—invariably with negative results. Nelson (1949), on the other hand has succeeded with a tissue suspension of human spleen in provoking reaction papules in sarcoid patients. In his later investigations he has succeeded only partially in corroborating his first findings (personal communication). His tests with coagulated egg albumin, with normal muscle tissue, and normal lymph nodes gave negative results as did also suspensions of *Pityrosporon ovale* calcium sulphate, particles of collodion, and oil-free soya bean phosphatides.



Fig. 25.—Kveim's reaction. Sarcoid-like infiltration 2 years after the injection of the antigen. The histological changes are similar to those seen in sarcoidosis nodules which have arisen spontaneously



Fig. 26.—Kveim reaction. 1, 2, 3 and 4 are reactions to different suspensions of sarcoid tissue. 5 and 6 are sarcoid nodules which have arisen spontaneously. 2 and 5 showed the same histological picture.

Wade (1951) has obtained negative results with the lepromin reaction in a few cases of sarcoidosis.

There do not seem to be any definite observations showing that the employment of tissue suspensions other than those of sarcoid tissue can provoke reaction papules of the type to be seen when Kveim's reaction is positive. An exception to this conclusion is the above mentioned observation by Nelson.

Skin reactions provoked by suspensions of corpuscular substances

It has long been known that foreign bodies such as small mineral particles can cause granulomas having histological structures closely resembling sarcoid infiltrations. The reaction of the human body to beryllium compounds has attracted great interest. In 1948 the *Journal of the American Medical Association* published a symposium on this matter and since then Neave, Frank, and Tolmach



FIG 22.—Papules following the injection of suspensions of sarcoid tissue (Kveim's reaction) K 1 = Antigen 17 4½ months old K 2 = Antigen 18 2 months old K 3 = Antigen 19 1 month old M = Mantoux reaction after 2 days (negative) K 3—Biopsy of the lesion showed "Differentiated reaction"

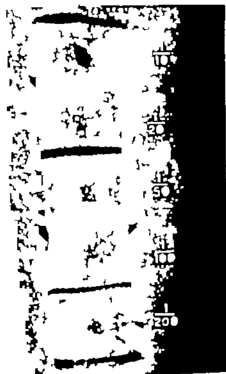


FIG 23.—Papules provoked by the injection of dilutions of suspensions of sarcoid tissue (Kveim's reaction) 6 months after the intracutaneous injection of the antigen



FIG 24.—Late papules, 2 months old, after diagnostic B.C.G reaction" showing "negative early reaction" Histological examination showed differentiated reaction (*See also* Fig. 22.)

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(1950) as well as others have contributed to our knowledge. Foreign-body granulomas have also been caused by salicylates. Gahlen and Klüken (1952) have recently recorded 2 cases of foreign body granulomas which, after a latent period of 5 and 8 years respectively followed a mining accident with gunpowder tatooing. Both patients showed signs of sarcoidosis, which malady according to these authors, should be regarded as a factor predisposing to foreign-body granulomas. A similar case has been observed in my hospital (Case IX)

Refvem (1947) has examined a series of sections of chronic granuloma in the intestinal tract, and among 209 cases there were 53 in which he demonstrated definite mineral elements with the aid of a polarizing microscope. Employing the same technique he has examined some 100 sections of sarcoid infiltrations, and in 4 cases he demonstrated mineral particles

The cause of foreign-body granulomas is to be sought in the provocative effects of the chemical and physical properties of certain particles, and in the special mode of reaction of the surrounding tissues. Ordinary tatooing with Indian ink and dyes seldom causes foreign-body granulomas, and the same may be said of gunpowder dust *deposited in the skin after mining accidents It is therefore most* interesting that several cases of granuloma formation due to this cause have been observed in sarcoidosis patients. This observation may be interpreted as showing that the tissues of these patients possess a peculiar mode of reaction—a "sarcoid reaction type.

Many experiments have been made with the purpose of provoking foreign-body granulomas in sarcoidosis patients by injecting particulate and other elements into the skin. In my hospital experiments have been made with catgut, and Refvem (1947) has worked with silicates Haxthausen (1948) has used talc and aleuronate, Schaumann and Seeberg (1948) Indian ink and paraffin oil whilst Nelson (1949) has experimented with calcium sulphate and particles of collodium. All these investigations have given negative results, and we may therefore conclude that experiments with various corpuscular elements have not yet shown that they are capable of inducing foreign-body granulomas in sarcoidosis patients *Further investigations must, however be undertaken before we can draw conclusions from these negative findings It is doubtful if sufficient attention has been paid, in the experiments hitherto carried out to the very long latent period which has often been required for the development of foreign body granulomas (see* Gahlen and Klüken, 1952)

TUBERCULIN SENSITIVITY KVEIM'S REACTION

In the preceding section a brief survey has been given of the cutaneous reactions of primary importance with regard to the aetiology and pathogenesis of sarcoidosis. Though the remarkably frequent anergy to tuberculin or the weak tuberculin sensitivity of sarcoidosis patients has for a long time attracted much attention we still lack a satisfactory explanation of this phenomenon. *It must be assumed* that the tuberculin sensitivity which is weak or has ceased to exist is an expression of some feature of the pathology *of sarcoidosis even though similar conditions in a* considerably less marked degree may also be observed in other diseases. At any rate the *demonstration of an anergy or low tuberculin sensitivity* must give some support to the diagnosis of sarcoidosis. On the other hand the demonstration

of these qualities cannot be invoked to show that sarcoidosis depends on a tuberculous infection nor to provide convincing argument against this opinion.

The experiments with BCG inoculations of sarcoid patients may to a certain extent invalidate the argument in favour of a tuberculous aetiology for in most sarcoid patients the same type of skin reaction is to be obtained as that observed in BCG inoculation of tuberculin-negative healthy persons (late reaction). Certain observations seem, however to show that it is more common for sarcoid patients than for tuberculin-negative healthy persons to react to BCG inoculation of the skin by indolent papules at the site of inoculation, papules which present a certain similarity both clinical and histological, to the sarcoid nodules which develop spontaneously

Very interesting also are Warfvinge's (1945) observations of a "sarcoid" tissue reaction following the injection into the skin of killed tubercle bacilli in cases of sarcoid The importance of this observation as a diagnostic test is, however considerably reduced by Björnstad's (1948) control test by which he showed that a similar sarcoid reaction can also be evoked by the intracutaneous injection of killed tubercle bacilli into tuberculin-negative healthy persons.

At present it would seem that heat-sterilized suspensions of sarcoid tissue provide the only "antigen which, in about 90 per cent of cases, provokes a typical persistent papular reaction in sarcoid patients (*Kveim's reaction*). On the other hand, in other persons the same "antigen usually fails to provoke any clinical or histological tissue reaction of a similar type.

We still do not know the basis of Kveim's reaction and the following possibilities must be considered Kveim's reaction depends on a specific allergy *in* sarcoid patients or it depends on the existence of tuberculin-like substances in tissue suspensions or it is an expression of a sarcoid mode of reaction

The first possibility that Kveim's reaction is an expression of an allergic reaction in sarcoid patients to specific substances in the tissue suspension ("antigen") seems to be the most plausible explanation. We must, however insist that up to now we know of no other allergic skin reaction with reaction papules developing after so long a latent period and persisting for months and even years, and presenting the clinical appearance and histological structure so closely resembling the spontaneous skin manifestations of sarcoidosis. Leider (1948) states that Sulzberger has suggested another explanation. According to this hypothesis, the appearance of Kveim's reaction depends on a capacity peculiar to sarcoid patients, to become sensitized by the tissue suspension. It is the "antigen which, after the injection into the skin, sensitizes it, and then after an incubation period of variable length, favours the development of a sarcoid" tissue reaction. The incubation period needed for the development of Kveim's reaction seems to be shortened by repeated tests—an observation which may support this hypothesis.

The second possibility that Kveim's reaction is due to the presence, in the sarcoid tissue suspension, of killed tubercle bacilli or tuberculin-like substances, has been supported by several investigators (Warfvinge, 1943 1945 Schaumann and Seeberg, 1948 Leider 1948). Here let it again be noted that ordinary methods have failed to reveal tubercle bacilli in sarcoid tissue. The most important argument against the theory that the active principle in suspensions of tubercle bacilli (killed tubercle bacilli and live BCG) is identical with the Kveim antigen is that in tuberculin-negative healthy persons the action of these antigens is different in

principle. While tuberculin negative healthy persons do not usually react to an injection of sarcoid tissue suspensions, injections of BCG given to the same persons will as a rule, *provoke a clinically demonstrable late* reaction (at any rate with maculation)

The third possibility that Kveim s reaction is the expression of a sarcoid mode of reaction Köbner phenomenon" an "isomorf Reiz effect" has formed the basis for the extensive tests which have been carried out on sarcoid patients with other tissue suspensions (Frei s antigen, lepromin antigen, normal spleen) and with corpuscular particles (beryllium, silicates, calcium salts, talc) As already pointed *out in detail, these investigations have on the whole* given negative results.

The observations hitherto made on the basis of quite comprehensive experimental investigations suggest that Kveim *s reaction is most likely an allergic process, for* the sarcoidosis as such has either induced a specific allergy or has created an increased capacity on the part of the skin to become sensitized by the injection of a heat sterilized suspension of sarcoid tissue.

It may therefore be assumed that suspensions of sarcoid tissue contain unknown specific substances which are responsible for the development of this skin reaction

THE AETIOLOGY OF SARCOIDOSIS

The aetiology of sarcoidosis has been the subject of comprehensive investigations for more than half a century yet this problem remains unsolved. Opinions concerning causal factors are widely divergent, and there is no unanimity of opinion concerning the significance that should be attached to the various pathological observations which have been made in this disease.

There are three theories which come foremost the disease is tuberculous or it can be provoked by many different factors owing to an individuality-determined sarcoid mode of reaction or it is an infectious disease of viral origin.

In his latter publications, Boeck (1916) was inclined to regard the disease as a form of tuberculosis—a point of view subsequently maintained by several other observers. Of late years, many histological factors not usually associated with tuberculosis have been demonstrated by Longcope and Freiman (1952) Jaques *(1952) and others. Yet it must be admitted that even a very experienced* pathologist cannot in a given case definitely say that a "sarcoid like" tissue can only be a sarcoidosis and he cannot dismiss the possibility of tuberculosis. With his great experience, in studying the histology of sarcoidosis, Kreyberg is in the habit of reporting on a histological section, even when it presents the features considered as characteristic of sarcoidosis, in the following way "*Boeck s sarcoid* probable, tuberculosis cannot be excluded It must be the clinician s task to *diagnose sarcoidosis also on the strength of other signs* and symptoms.

In most reviews of the aetiology of sarcoidosis, reference is made to certain observers who have demonstrated tubercle bacilli in sections of "sarcoid" tissue. A few positive culture and inoculation tests for tubercle bacilli, with material supposed to be sarcoid tissue, have also been reported On the other hand many comprehensive and carefully executed *inoculation and culture tests have yielded* negative results Pautrier (1948) for example, has written "I have never been able to obtain a positive inoculation from sarcoid tissue in any of the cases I have investigated personally The many similar tests carried out at my hospital have

yielded the same negative finding. As for the few positive findings of tubercle bacilli in cases of sarcoidosis, Longcope and Freiman (1952) comment that "this conclusion does not rest firmly upon Koch's postulates"

Supporters of the view that sarcoidosis is of tuberculous origin attach importance to the fact that now and then bacillary pulmonary tuberculosis is demonstrable in a patient who has had, or still has, manifestations of sarcoidosis (Schaumann, 1924 Warfvinge, 1945 and others). To this one may answer that bacillary tuberculosis may also occur among anergic persons. Besides, pulmonary tuberculosis may develop in a sarcoidosis patient, and at my hospital a characteristic case of this type has been observed by Bjornstad (1948). It would be difficult to prove in any case that there had been an evolution from sarcoidosis to tuberculosis and *vice versa*, for it is common knowledge that we cannot with absolute certainty always be sure of our diagnosis of sarcoidosis The evidence presented by clinical findings have no great weight when we investigate the possibility of tuberculosis as a cause of this disease.

Post mortem examinations of sarcoid patients often reveal tuberculous changes in the lungs. In their survey of this problem, Longcope and Freiman (1952) stated that tuberculosis had been found in 15–25 per cent of the post-mortem examinations of sarcoid patients. There are many elements of uncertainty when we try to estimate the value of these observations for example was the clinical diagnosis of sarcoidosis reliable, and may both sarcoidosis and tuberculosis have existed simultaneously in one and the same patient without necessarily being manifestations of the same causal factor? Post-mortem findings have not helped much to throw light on the aetiology of sarcoidosis.

As already noted, Jadassohn advanced his well-known theory concerning positive anergy" in order to explain the surprising fact that most sarcoid patients lost their tuberculin sensitivity or that their reaction is "weak" "Positive anergy" was interpreted as an "acquired anergy" supposed to indicate the existence of large quantities of tubercle bacillus antibodies, that is the outcome of the tuberculous element causing sarcoidosis. The demonstration of "antikutins" has yielded contradictory results. The most important support given to Jadassohn's theory is to be found in the experimental investigations of Lemming (1940) and Warfvinge (1945), who inoculated sarcoid patients with BCG and gave them injections of killed tubercle bacilli. Leider (1948) and Leider and Hyman (1950) have discussed these problems very thoroughly in several publications. But further investigations of this kind are necessary for it would seem that hitherto a sufficient number of control tests of tuberculin-negative healthy persons have not been carried out.

Many points concerning the meaning of positive anergy as an expression of immunity require clarification. Positive anergy is still a theoretical conception, and we must of course be very cautious if we are to cite one theory as "evidence in favour of another theory—that of sarcoidosis being an expression of tuberculosis.

It must be noted that sarcoid-like manifestations may occur as an expression of other known infections. Danbolt and Brandt (1938) have isolated tubercle bacilli of an avian type in such a case. Sarcoid-like infiltrations can be found in tuberculosis, leprosy and syphilis. When we reflect that foreign-body granulomas may also present a sarcoid like clinical picture, it seems natural that many investigators regard sarcoidosis as being, perhaps, the expression of a special mode of reaction

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on the part of the person concerned In other words, like Curtis and Grekin (1949) they are inclined to believe in the multiple causes theory of aetiology Nevertheless it is remarkable that many patients with foreign body granulomas have been found on closer examination to present manifestations of a general sarcoidosis. As already pointed out, many experimental investigations have been undertaken to provoke "sarcoid" lesions by introducing organic and inorganic foreign bodies into the skin The results of these tests have hitherto been negative except with suspensions of sarcoid tissue (Kveim's reaction)

The third theory that the disease is a special infection of unknown aetiology possibly a virus, is founded in part on clinical observations. The chronic course run by the disease emphasizes its similarity to other chronic infections such as tuberculosis, syphilis and leprosy It would seem that the same conclusion could be drawn from the fact that heat sterilized suspensions of sarcoid tissue are capable of provoking infiltrations whose clinical and histological features appear to be identical with spontaneous sarcoid infiltrations (but which gradually disappear spontaneously) Kveim's reaction resembles in many respects Frei's reaction, the lepromin reaction and the luetin reaction. Hitherto as already pointed out, no other antigens have been found to possess the same properties as suspensions of sarcoid tissue In this connexion reference must be made to Löfgren and Lundbäck (1950) who as already noted, have succeeded in isolating a virus from sarcoidosis patients

The observations hitherto made concerning the aetiology of sarcoidosis, and the experimental tests carried out to throw further light on this problem have yielded such conflicting results that it is impossible at present to draw any definite conclusion, but it seems to me that the evidence in favour of an infectious aetiology is particularly weighty

THE DIAGNOSIS OF SARCOIDOSIS

Sarcoidosis is a systemic disease which provokes a reticulo-endothelial reaction showing a preference for organs containing much reticulo-endothelial tissue. The signs and symptoms of this disease can, however resemble those of other morbid processes. It follows that when sarcoidosis is confined to one or a few body areas or tissues, clinical diagnosis may be exceedingly difficult.

A pathological-anatomical examination of the morbid processes is of great importance to the diagnosis and can with certainty decide in a given case when these processes are not of a sarcoid character On the other hand a histological examination can give evidence indicating the probability of sarcoidosis But however important such an examination is to the diagnosis, we must insist that it can not by itself give us the final answer We must therefore accept with reserve the verdict to be found in many publications that the diagnosis was verified by biopsy"

Foreign body granulomas can present a histological structure very closely resembling that of definite sarcoid lesions. Here we must note that sarcoidosis cannot be diagnosed on the basis of such foreign body granulomas, for it is a systemic disease and the diagnosis depends on a definite pattern of signs and symptoms.

As already pointed out, when diagnosing sarcoidosis it is also important to keep in mind exactly what we mean by a tuberculous process. When it is reported that

the histological structure of a pathological specimen is compatible with the diagnosis of sarcoidosis, and when tubercle bacilli can be demonstrated on culture or inoculation, the lesion in question must be regarded as tuberculous. It is well known that in certain cases the cutaneous manifestations of sarcoidosis can be clinically indistinguishable from lupus vulgaris (*see* Case V). When tubercle bacilli are demonstrable by culture or inoculation, tuberculosis must be diagnosed even when the clinical picture and the histological structure could be interpreted as indicating sarcoidosis.

Anergy or weak tuberculin sensitivity is undoubtedly of very great importance in diagnosis but, as already noted sarcoidosis may occasionally be associated with positive tuberculin reactions, particularly when it is complicated by tuberculosis. Reversion from a previously positive tuberculin sensitivity to anergy in cases in which the clinical picture is suggestive of sarcoidosis, is to some extent indicative of this disease.

Kveim's reaction is of diagnostic value, and it is positive in about 90 per cent of clinically definite cases but with this skin test also we must expect a certain number of non-specific reactions (about 6 per cent). A positive Kveim test is therefore not enough in itself to confirm the diagnosis of sarcoidosis. Two drawbacks in the use of this test are that suitable material for the preparation of the antigen is not always available, and that at least a month must elapse before a reading can be taken of the test. But with a disease such as sarcoidosis, the diagnosis often requires prolonged observation, and Kveim's reaction is of great value even though we may have to wait for several months to be sure of the result.

The histological examination, tuberculin testing and Kveim's reaction are today the most important aids to the diagnosis of sarcoidosis. In most cases these examinations are necessary if we are to be sure of our diagnosis.

Sarcoidosis may also appear as a swelling of one or several of the superficial lymphatic glands, either as a solitary phenomenon or associated with lesions in other tissues. The disease can also manifest itself as *febris uveoparotidea*, as the Mikulicz syndrome or other rare morbid syndromes. In such cases the above-mentioned supplementary examinations (histological tuberculin tests and Kveim's reaction) will be necessary to establish the diagnosis.

In recent years growing significance has been attached to the intrathoracic localization of sarcoidosis where the disease may appear as swelling of the tracheal and hilar glands and infiltration of the lungs. In many cases a radiological examination can give useful diagnostic evidence, but when the disease is limited to the lungs or glands of the hilus or mediastinum, the radiological diagnosis can be accepted only as suggestive, the usual supplementary tests being necessary to clinch the diagnosis.

Osteitis cystoides (Jüngling) is not pathognomonic of sarcoidosis, but it is of great importance when it is associated with other manifestations of this disease.

The clinical diagnosis of sarcoidosis must be founded on as many signs and symptoms as possible, all of them pointing to this disease. The more numerous the signs and symptoms, the more certain the diagnosis. Kveim's reaction must be regarded as one of the most important single tests. But as long as the aetiology of the disease is not known, we shall often be confronted by cases of sarcoidosis having minimal manifestations, the certain diagnosis of which cannot be established by the criteria available today.

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It will thus be seen that when sarcoidosis is internal or deep-seated, the prognosis is not particularly good, chiefly because involvement of the lungs entails a great risk of the development of pulmonary fibrosis and also assuredly predisposes to pulmonary tuberculosis. As we may assume that sarcoidosis is a comparatively common disease, the discovery of its aetiology and effective methods of treatment are not only of scientific interest, but are matters of great importance to the welfare of the community

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TREATMENT

For several decades the treatment of sarcoidosis consisted of giving courses of arsenic combined, when the skin was involved with Finsen light treatment. While local Finsen therapy can undoubtedly hasten the absorption of sarcoid infiltrations, the value of arsenic is doubtful apart from its tonic effect.

Good reports have been received concerning the effects of calciferol but Nelson (1949) has not been able to confirm these optimistic views In my hospital, it has been abandoned for the time being, as its effects seemed to be doubtful and many sarcoidosis patients were found to be remarkably intolerant of the vitamin (Sundt, 1950)

Great interest attaches to the investigations made in recent years concerning the action of ACTH and cortisone on sarcoidosis, and many favourable accounts have been published concerning the effects of this treatment on both the cutaneous and pulmonary manifestations of the malady Lovelock and Stone (1951) Small (1951) Refvem (1952) and others At my hospital these hormones have been used in the treatment of 6 cases of cutaneous sarcoidosis. The lesions were seen to recede a trifle, but this remission was invariably transient.

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Sarcoidosis has been described as a benign disease, an adjective requiring many reservations. The cutaneous manifestations, to be sure, often disappear slowly in the course of several years, leaving a scarring or atrophic area Limited internal infiltrations can, however compromise the functions of the organ concerned and thus have serious consequences, as when the disease is situated in the heart, the nervous system the eyes and the endocrine organs. On the other hand, sarcoid involvement of internal organs such as the lungs may cause no symptoms, the disease being often discovered in the course of routine examinations of large groups in the community The behaviour of sarcoidosis of the lungs is of particular importance to the prognosis. Nitter (1953) has studied 90 patients suffering from sarcoidosis of the lungs (average observation period 5 5 years) He found that the miliary form of sarcoidosis of the lungs tended to end in complete remission in the course of 6–36 months Matters were different when the disease of the lungs consisted of diffuse or circumscribed coarsely patchy parenchymal opacities more than half of these cases developed signs of pulmonary fibrosis during the observation period, and one-third of them died of this condition In this group no definite regression of the diffuse or coarsely patchy parenchymal opacities was observed Pulmonary fibrosis must therefore be regarded as one of the most serious complications of sarcoidosis of the lungs.

With regard to the causes of death, Vosbein (1952) has recently made an estimate based on 140 cases already published He found that in 48 per cent, sarcoidosis

was probably the cause. Of 67 persons who died of this disease 51 per cent died because of pulmonary involvement, 25 per cent from invasion of the central nervous system, and 17 per cent from involvement of the heart and other organs. Among the 75 sarcoidosis patients whose deaths were presumably due to causes other than sarcoidosis, pulmonary tuberculosis was the cause of death in 42 per cent, and vascular and other diseases in 8 per cent.

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CHAPTER 9

A CRITICAL APPRAISAL OF MODERN TRENDS IN LEPROSY WITH PARTICULAR REFERENCE TO ADVANCES IN IMMUNOLOGY HISTOPATHOLOGY AND TREATMENT

R. G COCHRANE

WITHIN the last decade very great and significant advances have been made in the understanding and treatment of leprosy To appreciate fully the modern trends and the significance of the most recent work the subject will be discussed under the following sub-divisions

Epidemiology and bacteriology including immunology
Classification and diagnosis
Therapy
Criteria of cure.

EPIDEMIOLOGY AND BACTERIOLOGY (INCLUDING IMMUNOLOGY)

As a result of two observations within recent years questions with regard to the mode of introduction of *Mycobacterium lepræ* and the infectivity of the disease have once again been raised. The first was the discovery that a certain proportion (10–20 per cent) of healthy contacts of open cases showed *Myco lepræ* in very small numbers in the skin lying as inert bodies at the junction of the pars papillaris and pars reticularis. The second observation was that in the so-called closed cases, that is those in which bacilli could not be discovered by standard methods of examination, by careful study of serial sections or by a concentration method suggested by Khanolkar (1951) and modified by Figuerdo (Figuerdo and Desai, 1952) and later by Dharmendra (Dharmendra and Chatterjee, 1952) bacilli, sometimes in appreciable numbers, could be detected. This work, therefore, suggests that, if our technique is adequate, in every active case of leprosy *Myco lepræ* should be demonstrable. The whole question then of the infectivity of the closed case has been re-opened. While some workers believe that every active case of leprosy must be considered infective, others consider that this work does not modify the opinion, generally held, that it is the open case (that is, the case from which *Myco. lepræ* can be discovered by standard methods of examination) that is infective and an actual or potential danger to healthy members of the community particularly children It is the author's opinion that, if meticulous search and enquiry is made, in all cases of leprosy the open case could be discovered, for the more accurate the history and the more detailed the examination of contacts the greater are the chances that the source of infection will be traced. Further wherever there has been effective segregation of the open cases, particularly preventing night contact with children, there has been evidence that leprosy can be controlled by this means The clan segregation system devised in Nigeria, and the night segregation experiments in Southern India are examples of the control of

leprosy by this means It is not denied that the so-called "closed" case is absolutely incapable of infecting others, but it is contended that the possibility of this is so unlikely that such theoretical considerations should not affect the well-established methods of public health control of the disease.

The work particularly that of Khanolkar (1951) which demonstrates that *Myco leprae* first appears in the small superficial nerve plexuses of the skin, suggests that the skin is probably the mode of entrance of the organism, and that this predilection for nerves in the early initial phases points to the possibility that *Myco leprae* can only become pathogenic in man after passing through the superficial nerve plexuses of the skin This suggested passage" through the nerve tissues opens up intriguing possibilities in relation to fresh approaches in the attempt to cultivate the *Myco leprae*

Within recent years, as the result of the refined methods of preparing lepromin devised by Fernandez (1940) and Dharmendra (1940) opportunities have occurred for the more detailed study of the tissue reactions in persons not only with leprosy but in those who are in contact with leprosy cases. This gives general support to the opinion expressed later that in all probability all persons who come into contact with leprosy pass through a positive lepromin phase. This has given rise to the study of the antigenic properties of *Myco tuberculosis* in relation to leprosy The observation of the South American workers particularly Nelson de Campos (1950) and in the work of Chaussinand (1950) in French Africa that BCG vaccination will cause a negative lepromin reaction to become positive is of significance. Lowe (1952, 1953) in Nigeria has recently confirmed this observation. It has therefore been suggested by Muir and other workers that BCG vaccination should be used for immunizing large sections of the population in the campaign to combat the disease There are, however several questions that arise with reference to this (1) If as is probable, all persons pass through an initial positive lepromin phase, how long does this phase continue? (2) Next what are the factors that cause the reversibility of the lepromin reaction? (3) Lastly and this is the most important question, what is the relationship between a positive lepromin and immunity? In other words, it is doubtful whether tissue sensitivity bears any real relationship to immunity

It must be remembered that while a lepromin positive reactor may have no actual immunity against an attack of leprosy there is an increased likelihood if the disease develops that such a person will show the highly resistant tuberculoid form of leprosy Before any conclusions could be drawn with reference to the relationship of immunity in leprosy and the lepromin test a very long-term (5–10 years) experiment among a relatively stable population with a high incidence of leprosy would have to be planned

CLASSIFICATION AND DIAGNOSIS

Classification

In this connexion it must be stated categorically that the lepromin test is of no help in the diagnosis of leprosy This test is only a measure of the actual or potential tissue immunity of an individual presumably infected by *Myco leprae* In other words, as in tuberculosis so probably in leprosy a positive skin test indicates that the individual is harbouring the pathogenic organism within the tissue

—dead or alive. The person may be in the silent phase of the disease, show active disease, or be a resolved case. The conclusions drawn by some workers that tuberculosis confers an immunity against leprosy needs further proof The lepromin test, however has proved a very great aid in the study of the different types of leprosy and is almost indispensable if a right classification and a reasonably accurate prognosis are to be given in any particular case of leprosy

The South American work, more especially the earlier work of Pardo-Castello and Tiant (1943) on the polar conception of leprosy is fundamental to our understanding of the disease This, as well as subsequent work, envisages a stage when the lepromin is not only strongly positive but irreversible. Schujman (1950) states that in his own opinion he has never seen a strongly positive lepromin reaction become negative. If this conception is true then it is probable that at some time or another every person who has become infected with *Myco lepræ* (that is the organism of leprosy has been introduced into the system, presumably through the skin) develops a positive lepromin reaction. It is known that all lepromatous cases, and a fair proportion of macular (indeterminate) and polyneuritic cases, show a negative lepromin reaction, whereas in others, particularly the frank tuberculoid (lepride) group, the reaction is very strongly positive, going on in some instances to ulceration. Where and when this sensitization takes place has not been established, and it is presumed that this immunity develops as the result of the introduction of the specific organism (*Myco lepræ*) into the skin. It then follows that one of three developments can take place (1) The tissues may become *hyper sensitized* (2) the tissues may become *desensitized* or (3) they may remain in an unstable position, not fully sensitized, and not completely desensitized. *If this* concept is correct then all clinical manifestations of leprosy should *show one of three immunological* reactions, a strongly positive reaction, a weakly positive, and a completely negative response and leprosy should be divisible into three primary groups or types for clinical purposes (*a*) Tuberculoid (lepride) (*b*) lepromatous and (*c*) border line (dimorphous) All lesions, therefore, should fall into one or other of these groups, and there should strictly speaking, be no indeterminate classification as suggested by the South American workers. The only period which could accurately be considered as indeterminate is Khanolkar's "silent phase before lesions have actually developed, or when the lesion is so early that it cannot be diagnosed apart from finding *Myco lepræ* in the skin by special techniques, for example, concentration or by the careful study of serial sections. Basing classification on this fundamental concept, let us consider that all lesions of leprosy are divisible into these three primary groups, and discuss the possibility of reversibility of types

Clinically leprosy can be considered as macular infiltrative, and polyneuritic, and we will review these lesions in the light of the above statements, and thus indicate the modern trend in classification of this complex disease.

Macules

On studying the macules of leprosy in detail clinically they can be divided into (*a*) those which tend to be small with vague edges, the periphery fading into the surrounding normal skin (*b*) those which tend to be large, with a characteristic distribution and a periphery which is sharply defined. The spreading edge can be quite clearly seen and (*c*) there is, however a third type of macule which is difficult

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tiated bacilli usually are moderately numerous in the nerves and are arranged as in the lepromatous group some nerves show definite cellular infiltration while others show perineural cuffing and endoneural proliferation. In other words, these macules are in a stage of unstable equilibrium. Their evolution has not been determined, but one hazards an opinion that they either become markedly active and show all the signs of a fully developed dimorphous lesion or pass into the lepromatous stage.

In macular lesions of leprosy one must consider the frankly lepromatous macule This is a development from the early macule with hazy or indefinite outline, and the histological picture is merely an advanced stage of that which has already been described. Macrophages are the predominant cells and these may replace almost entirely the round cells. There is evidence of the formation of a free sub-epidermal zone. The nerves usually are easily recognized, and there is perineural and endoneural proliferation, giving rise to the characteristic "cuff like appearance. There is usually some evidence of hyaline changes in the nerve. Clinically the lesions are still macules, but they are more erythematous and more easily seen in good light than in the earlier variety

Bacilli can usually be demonstrated by standard methods of examination whereas in the earlier lesions they can only be found by special techniques for example, by biopsy or concentration methods.

Clinically these three varieties of macules illustrate well that all leprosy probably belongs to one of three basic groups—tuberculoid (lepride), border-line (dimorphous) and lepromatous. These groups or types are determined by their clinical, histological and immunological features and represent the three responses to lepromin, namely strongly positive, weakly or variably positive, and negative, and indicate the three immunological states—(i) a state of hypersensitivity (ii) a state of unstable equilibrium and (iii) a state of desensitivity We, therefore, maintain that to introduce the nomenclature of indeterminate is both misleading and erroneous, and that all the macules in this group will be found, in reality to belong to one of the above three categories.

The chief objection to classifying macules in this manner is that the dimorphous or border-line macule has not been sufficiently studied to enable it to be diagnosed apart from histology and the lepromin reaction. This, to our mind, is not a reason for ignoring the possibility of its occurrence. As has been emphasized previously all lesions should be classified according to the tissue response as shown by the lepromin test, and, therefore, macular lesions would come under the following heads

Positive lepromin	*Weakly positive or variable lepromin*	*Negative lepromin*
Tuberculoid (lepride)	Dimorphous macular	Prelepromatous macular
Maculo-anaesthetic		Lepromatous macular

To classify all macules clinically except those which show bacilli on standard methods of examination, as indeterminate seems to us unsound for careful study would, we feel, enable workers to place them into one of these, as we consider primary groups It will be noted that we have avoided, and will continue to avoid,

to describe and not yet generally accepted as such The lesions tend to be small the texture of the skin is different and tends to look wrinkled or atrophic, but the edge of the lesion is less defined than in the second group but not as indefinite as in the former Histologically these three macules, I believe, will be found to vary in certain important features, and thus give support to the contention that they form the three primary groups. Let us consider the histopathological picture in these three groups.

Lepromin test strongly positive—These, generally speaking, are the macules—using the term in the strictly dermatological sense—with well defined and clear cut margins The infiltrative process usually of round cells, is definitely focalized under the epidermis, and these foci are more clearly seen around the appendages of the skin (for example vessels sweat glands) The small nerves in the corium show changes which are mainly infiltrative In other words the round cells and macrophages (? epithelioid cells) are actually invading the substance of the nerve. In the more developed macule there are seen definite epithelioid foci, both around the appendages of the skin and within the nerves themselves *Myco lepræ* when present tend to be few and do not show the characteristic appearance as described by Khanolkar of fish swimming up-stream" While generally speaking, the histological picture fits in with that described by the South American and other workers as "simple inflammatory" the more marked changes would be classified if not clinically at least histologically as tuberculoid.

Lepromin negative—Lepromin negative macules are the typical uncharacteristic or indeterminate macules of the South American classification Histologically only simple inflammatory change is seen and the round-cell infiltration is minimal. There is no tendency for the infiltration which is always slight, either in the superficial layers of the corium or around the appendages of the skin, to be grouped or focalized The cellular exudate consists mainly of round cells and a few histocytes. The nerves are not invaded although there may be some perineural "cuffing" as seen characteristically in the lepromatous group It is usually impossible to diagnose these macules histologically unless bacilli are found, and when seen they tend to show the "fish swimming up-stream" appearance In other words, as in the lepromatous group the tissues show no response to the bacillary invasion and are in a complete state of desensitization

Macules associated with a slightly positive lepromin reaction—In the macular stage of leprosy it is not always easy to determine whether an individual case is likely to develop into a frank tuberculoid (lepride) or a definite lepromatous case, and, therefore for this reason, the tendency has been to place the majority of macules in the indeterminate or uncharacteristic group We believe, however this is misleading and consider that the macules which are doubtful in all probability should be classified as border line or dimorphous preferring the latter term, because its meaning is less equivocal After much study of these macules there appears to be a group in which both characteristics, the lepride and the leproma are apparently seen There is a general tendency to focalization The areas of infiltration, while scattered in the corium appear to have a definite pattern and there is a marked concentration of the granulomas around the hair follicles There may be epithelioid cells, or the macrophages may be undifferen-

TABLE I

Histopathological Differences between Tuberculoid, Dimorphous and Lepromatous Leprosy

Tuberculoid	*Dimorphous*	*Lepromatous*
Definite focalization of granulomas, with epithelioid and giant-cell foci associated, chiefly around the appendages of the skin	(a) The infiltration tends to be more diffuse, although in the deeper parts of the corium there may be the appearance of foci (b) There are usually epithelioid and giant cells associated with macrophages, which may show all the features up to fully developed Virchow cells	( ) There is no evidence of focalization. (b) Round cells tend to be replaced by macrophages (lepra cells) and many of these show commencing vacuolation (pre-Virchow cells), or gross vacuolation (Virchow cells)
The infiltration presses up against the epidermis leaving no free epidermal zone	In the well developed case there is a free and usually vascular sub-epidermal zone	There is a characteristic free sub-epidermal zone
(a) The nerves are seen to be invaded, sometimes grossly and with cellular infiltration in which there are epithelioid and giant cells (b) There may be necrosis or actual caseation of the nerves (c) The nerve fibres are sometimes seen as characteristic remnants amongst the granulomatous masses	(a) The nerves show varying stages of involvement, from those which are grossly invaded to ones comparatively free (b) There may be hyaline change	(a) The nerves are not invaded, but there is perineural and endoneural infiltration, giving rise to the characteristic "cuffing" appearance (b) There is usually hyaline degeneration
Bacilli are absent or few in number	Bacilli are usually fairly numerous and are seen within the nerves, showing the fish swimming upstream appearance—with the general picture of lepromatous leprosy	Bacilli in large numbers and free in the nerves, showing the fish swimming upstream appearance

Polyneuritic lesions

It is generally accepted that there is a polyneuritic group of cases, which show only polyneuritic signs, with no accompanying macules or other skin lesions. It is also generally accepted that the polyneuritic cases can be divided into those which are lepromin positive and those which are negative. The former it is suggested, should be classified under the polyneuritic tuberculoid group the latter under polyneuritic leproma The histopathology of these two groups has not been worked out, and if there exists the *pure polyneuritic case, it probably represents* that type of individual in whom the bacilli *remain in* the nerves and have not burst into the corium of the skin

In polyneuritic leproma there is evidence that the bacilli in the nerves behave as in lepromatous cases—that is they are seen in relatively large numbers within the nerve, with a varying amount of cellular infiltration and show the "fish swimming up-stream "appearance. In polyneuritic tuberculoid leprosy in the few sections which have been studied it appears that the nerves are free of bacilli, but small

the use of the term neural. The work of Khanolkar (1951) indicates that all leprosy is neural and alterations in sensation depend on the amount of damage to the conducting mechanism either through direct cellular invasion or as the result of the damage produced by the bacilli or their metabolic products, within the nerve.

Infiltrated lesions

Following the principle of relating the clinical condition to the lepromin reaction, the three main groups of lesions can be classified according to their lepromin response. The strongly positive lepromin reactions show the classical manifestations of tuberculoid leprosy (leprides) of either minor or major degree. These lesions are so familiar to all that they do not need description Similarly the infiltrated lepromatous lesions have for long been accepted and have been divided into the diffuse, the infiltrated and the nodular lepromatous sub-types. These lesions are simply a further development, both clinically and histologically of the lepromatous macule. It is the lesions which show a slightly positive, or variable, response to lepromin that have caused confusion As far as these infiltrated lesions are concerned there has been an increasing tendency to accept them as a separate group and the terms border line intermediate, dimorphous, atypical, have all been suggested Personally we contend that dimorphous is the most convenient term for these lesions. Border line is unsatisfactory as are also intermediate and atypical None of these concisely defines the characteristics of this group Dimorphous we believe, gives in one word the features of the group better than any other term and we hope that it will be accepted as a suitable term for general use in classification The characteristics of the border line or dimorphous lesions are those of both the leprides as well as the lepromatous types. Clinically the lesions show infiltration, while this infiltration may be gross or slight The demarcation of the periphery of the lesion is not clear In the less marked cases the infiltration is slight but shiny and with a tendency to desquamation or scaliness In the marked lesions there is gross infiltration a succulent appearance and an edge which fades into the surrounding normal skin and does not show the clear definition of the tuberculoid lesions Table I gives a brief description of the histopathological differences between the tuberculoid, the dimorphous and lepromatous leprosy It is, in our opinion, extremely important to recognize the dimorphous lesions because as the tissues are in an unstable immunological condition very violent tissue destroying reactions are liable to be seen particularly if sulphone therapy is pressed, resulting in gross deterioration of the condition and gross deformity In the pre-sulphone days the great majority if not all of the cases in this group became lepromatous and the end result was pathetic indeed. With judicious sulphone therapy and taking great care not to precipitate reactions, the outlook is altogether more favourable. The following is a summary of the suggested classification of the infiltrated lesions.

Lepromin positive	*Lepromin variable or weakly positive*	*Lepromin negative*
Tuberculoid (lepride)	Dimorphous	Lepromatous
Minor tuberculoid (lepride)	Atypical tuberculoid (lepride)	Diffuse
		Infiltrative
Major tuberculoid (lepride)	Atypical leproma	Nodular



FIG. 27.—Typical lesion of tuberculoid leprosy



FIG. 28.—Active major tuberculoid leprosy (*By courtesy of the Oxford University Press.*)



FIG. 29.—Atypical lepride. (*By courtesy of the Oxford University Press.*)

groups or clumps of *Myco leprae* may be seen in the exudate, which consists of round cells (lymphocytes) and epithelioid cells As far as is known no example of a polyneuritic dimorphous lesion has been met The nearest example is a section shown to the author by Khanolkar in which the great auricular nerve showed what appeared to be a dimorphous change. The skin section from the same case was similarly diagnosed

If then, it is assumed that there are three initial main groups of leprosy a classification to include these groups could be illustrated diagrammatically as shown in Table II

TABLE II

CLASSIFICATION OF THE THREE INITIAL OR MAIN GROUPS OF LEPROSY

I Indeterminate lesions	(*a*) Silent phase (*b*) Very early lesions (macules) impossible to diagnose apart from highly specialized techniques	Lepromin reaction usually positive—rarely negative
II *Lepromin positive*	*Lepromin variable or weakly positive*	*Lepromin negative*
Tuberculoid or lepride	Border line, atypical or dimorphous	Lepromatous
Macular lesions (*a*) Maculo-anaesthetic or lepride (*b*) Tuberculoid macular (lepride)	Dimorphous–macular lesions	Macular leproma (*a*) Pre-lepromatous macular (*b*) Lepromatous macular
Infiltrated lesions (*a*) Minor tuberculoid (lepride) (*b*) Major tuberculoid (lepride)	Infiltrated dimorphous lesions (*a*) Atypical tuberculoid (lepride) (*b*) Atypical leproma	Infiltrated leproma (*a*) Diffuse leproma (*b*) Nodular leproma
Polyneuritic tuberculoid (lepride)	*Dimorphous–polyneuritic*	*Polyneuritic leproma*

While it is believed that this scheme of classification covers all the lesions of leprosy yet it must be said that no one classification has yet been accepted and many workers would prefer to divide all lesions into four groups (*a*) Indeterminate (*b*) tuberculoid (*c*) lepromatous and (*d*) polyneuritic. The indeterminate lesions would include all macular lesions showing a simple inflammatory change in section and without definite tuberculoid features histologically That is, there would be no attempt at differentiating the various types of macules described above. Tuberculoid lesions would be divided into major and minor and subdivided according to their dermatological appearance, for example, papillate, circinate, plaques, nodules, and so on The lepromatous lesions would consist of macular lepromatous lesions, diffuse, infiltrated and nodular The border-line cases are those lesions which have been described above as dimorphous. The polyneuritic group, it is suggested should be subdivided into polyneuritic leproma and polyneuritic tuberculoid, according to the results of the lepromin test

At a meeting of the World Health Organization in November 1952 the Committee on leprosy recommended four basic groups in the classification of the malady—indeterminate tuberculoid, border line, and lepromatous.

In a good light a blunt but narrow-bladed scalpel is introduced and the internal septum is scraped sufficiently to remove a small piece of mucous membrane and this is transferred on to a slide and teased out so that a uniform smear is obtained. It is sometimes preferable to use a speculum when there is doubt, or when examination reveals a definite lesion in the nose.

The instrument we use for taking nasal smears, which was suggested by Wade of the Philippine Islands, is a looped paper-clip straightened out and the end hammered sufficiently to form a small scoop. This is then fixed into a piece of wood or bamboo to act as a handle and forms a very convenient inexpensive instrument for the purpose

Recently concentration methods and the so-called biopsy-smear technique have been described by the Bombay workers.

Histopathological diagnosis

In any doubtful lesion in leprosy a diagnosis should not be established unless bacilli have been found, either by one or other of the above techniques or in section. The author is of opinion that if the histological picture is not definite and bacilli cannot be found in sections or by special techniques, then the diagnosis of leprosy cannot be established. In this connection it must be remembered that special techniques are necessary for the detection of acid-fast bacilli in section, and the search for them needs patience and time.

Tissues are preferably fixed in Zenker solution, but should not remain in this fixative more than 5 hours. They are then washed for 12 hours, or overnight. Acid-fast bacilli in section should be stained by the Fite Faraco technique which is as follows

1 Deparaffinize sections with two changes of a mixture of 1 part of cotton seed, peanut or olive oil and 2 parts of xylol.

2. Drain, wipe back and sides, and blot section with filter paper

3 Treat with (aqueous) Lugol's iodine solution and with 5 per cent sodium thiosulphate solution to remove mercury precipitate from the Zenker solution.

4 Wash in water

5 Stain for 15–20 minutes in Ziehl Neelsen's carbol fuchsin at room temperature.

6. Decolorize for 1 2 minutes to a faint pink colour with 1 millilitre of concentrated hydrochloric acid in 99 millilitres of 70 per cent alcohol.

7 Wash in tap water

8 Counter-stain with Mayer's alum haematoxylin for 2 3 minutes, or alternatively with Gurr's aqueous methylene blue (1 per cent) ½–1 minute.

9 Wash in tap water till blue.

10. Decolorize with above acid alcohol if necessary (few seconds)

11 Blot with filter paper and keep in incubator at 37° C. over night.

12. Mount in clarite or similar synthetic medium.

Apart from finding of bacilli there are certain cellular changes in leprosy which are pathognomonic of leprosy These have been described previously It must be remembered that the sarcoids, lupus vulgaris, and lupus verrucosum, are liable to be diagnosed when the section is really one of leprosy It should be borne in mind that in none of these conditions are the nerves in the corium affected. The Masson technique, counter-staining with Saffron or the Mallory trichrome stain, will often differentiate nerves better than the standard haematoxylin and eosin method Fortunately in the dimorphous lesions, where real difficulties are likely

Diagnosis

While a classification is of great help in the diagnosis of leprosy the dermatologist is mostly concerned as to whether a given lesion is due to leprosy or not. There are in this connexion three methods by which a diagnosis can, in the majority of cases, be definitely established (1) Clinical (2) bacteriological and (3) histopathological

Clinical diagnosis

The following matters must be taken into account in diagnosing leprosy in a patient who seeks advice

(a) The type of lesion—macular infiltrated or nodular
(b) Loss of sensation—light touch pin prick or heat.
(c) Distribution of lesions—exposed surfaces
(d) Duration of lesions and previous treatment Have the lesions been present for several months without responding to standard treatment?
(e) Symptoms Do the lesions irritate, or are they symptomless?
(f) Are they associated with enlargement or tenderness of nerves or both?
(g) Is there any history of residence in an area where leprosy is endemic?

If a person states that the lesion—whether macular infiltrative or nodular—is of long duration, with loss of superficial tactile, thermal or pain sense if in addition, it has been present for some months and has not responded to ordinary lines of treatment, is symptomless and does not correspond to any common dermatological condition then leprosy must be suspected and other methods must be undertaken to establish the diagnosis. These methods are bacteriological and histological.

Bacteriological diagnosis

The standard method of establishing a diagnosis is by the slit-smear technique, first described by Wade (1935) and universally adopted. The following is a description of this procedure

1 Cleanse the area to be examined by rubbing briefly though vigorously with a small cotton-wool sponge with spirit. Wipe dry with cotton-wool

2. Pinch up the skin in fold, applying enough compression to stop or minimize bleeding. When it cannot be actually picked up compress it laterally as much as possible

3 With a properly cleansed scalpel of suitable style and size make a small but real cut 5 millimetres or so long and deep enough (about 2 millimetres) to get well into the infiltrated layer

4 If blood or lymph exudes in any quantity wipe it off With the knife-blade turned transversely to the line of cut, scrape the side and bottom of the cut repeatedly and with sufficient vigour to obtain a little actual tissue pulp from below the epidermis.

5 With the knife transfer the small amount of material obtained to a microscope slide to make a uniform and moderately thick smear over a small area Multiple smears from the same patient are best put on to a single slide

6. For after-treatment of the cut the patient is simply given a piece of cotton-wool to compress it until oozing stops. No dressing is necessary

In addition to taking a smear from lesions in skin a nasal smear should also be taken. The technique is as follows

milligrams twice weekly are given. Thereafter the dose is raised each month by 100 milligrams until the maximum of 400 milligrams twice a week is reached (800 milligrams per week in all)

If daily treatment is considered preferable commence with twice weekly treatment until 100 milligrams twice weekly is reached. After 14 days give 100 milligrams thrice weekly At the end of 14 days give this dose four times weekly and then increased until 100 milligrams six times a week (that is, every day except Sundays) is reached

When it is inconvenient to give tablets, or patients cannot be trusted to take the tablets, then subcutaneous injections of a suspension of dapsone can be given subcutaneously or intramuscularly The drug is made up as a suspension in groundnut or coconut oil with a small amount of antiseptic (phenol 0 5 per cent) sterilized, preferably by hot-air oven sterilization, and put into rubber-capped bottles A convenient suspension contains 20 per cent of the drug. It has been found satisfactory to give weekly injections commencing at a dosage of 100 milligrams per week and increasing by 100 milligrams monthly up to 500 milligrams per week. Some authorities recommend fortnightly and others twice weekly injections. If given twice weekly the commencing dose is 50 milligrams rising by 50 milligrams each fortnight until 400 milligrams twice a week are given.

Sulphetrone

It has been shown beyond reasonable doubt that sulphetrone by mouth is hydrolysed to the parent sulphone (DDS) and therefore this method of administration is wasteful and expensive and for these reasons is not recommended.

Sulphetrone parenterally however is probably the method of choice when side or toxic effects are feared, or when oral treatment is inadvisable, and close supervision of parenteral DDS is not possible. Suspensions of DDS are liable to precipitate on standing and, therefore the rubber-capped bottles should be warmed and vigorously shaken between individual injections. Care, then, must be taken to inject the correct dose, otherwise the first group of patients are liable to get the weaker suspension and later patients the more concentrated one Further regulation of dosages is much more simple with aqueous solutions and the trouble of unabsorbed masses is very much less likely to occur Parenteral sulphetrone is recommended rather than suspensions of DDS. The most convenient strength of sulphetrone solution is a 50 per cent aqueous solution, weaker solutions being more liable to break down to the parent sulphone on autoclaving. The dose is ½–3 millilitres twice weekly Commence with ½ millilitre twice weekly rising by ½ millilitre every fortnight until the dose of 3 millilitres twice weekly (3 grammes) is reached. There is evidence to show that smaller dosages (1–2 grammes per week) are as effective, but until this is definitely established these doses are not recommended

In the case of children the general rule with regard to dosage is for those of 7 years of age and under one-quarter of the adult dose above 7 years and not more than 12 years, one-half the adult dose.

Promin

This derivative of 4 4 diaminodiphenyl sulphone is mentioned, for it is the drug of choice in many institutions, particularly in South America and in Louisiana.

to arise, acid fast bacilli are almost invariably found in the sections. In the lepromatous group the presence of acid fast bacilli and the characteristic clear subepidermal zone establish the diagnosis

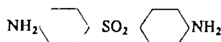
THERAPY

Leprosy after many decades in which treatment was in a large group of cases, of uncertain value, has at last joined those diseases which respond to chemotherapy

It can be said that the experimental stage is now passed and general guidance can now be given with regard to the most practical methods of therapy which will be considered under the following heads (1) Sulphone therapy (2) other chemotherapeutic agents (3) results of treatment (4) action of chemotherapeutic agents (5) criteria of cure and (6) reactions in leprosy and side and toxic effects.

Sulphone therapy

It has now become established that the sulphone group of drugs is the choice in all active cases of leprosy The basic drug in this group is diamino-diphenyl sulphone with a simple formula as follows



Diaminodiphenylsulphone (dapsone or DDS) is the therapeutic agent most universally used but owing to certain drawbacks, which will be mentioned, an alternative remedy should be available, and it is the writer's belief that the di-substituted sulphone sulphetrone should be dissolved in a 50 per cent aqueous solution and given parenterally It has been contended that disubstituted derivatives of DDS are inactive and only act by being broken down in the body to the parent sulphone It has been established that while the disubstituted sulphones when given by mouth are hydrolysed in the stomach and converted to DDS sulphetrone when given parenterally is broken down to a monosubstituted sulphone and probably acts as such Therefore, when considering an alternative treatment the most logical derivative to use is sulphetrone given parenterally

Methods of administration and dosage

The ways of administering the parent sulphone are oral and parenterally While it has now been definitely shown that in the dosages recommended dapsone is relatively non toxic, care must be taken when the drug is given orally that instructions are explicitly followed The following therefore is the regimen advised in the treatment of leprosy Dapsone can be given twice a week or daily While some workers state that dapsone is more effective daily it is always wise to commence with twice weekly dosage The course now to be detailed differs from that frequently recommended because, for the inexperienced or those dealing with certain racial groups—for example, Anglo-Saxon or Mongolian—or advanced types of lepromatous leprosy it is better to err on the cautious side.

Dapsone (DDS or 4 4 diaminodiphenyl sulphone)

The commencing dose is 25 milligrams orally twice a week—a three-day interval being given. The dose then is raised by 25 milligrams each fortnight until 100

milligrams twice weekly are given. Thereafter the dose is raised each month by 100 milligrams until the maximum of 400 milligrams twice a week is reached (800 milligrams per week in all).

If daily treatment is considered preferable commence with twice weekly treatment until 100 milligrams twice weekly is reached. After 14 days give 100 milligrams thrice weekly. At the end of 14 days give this dose four times weekly and then increased until 100 milligrams six times a week (that is, every day except Sundays) is reached.

When it is inconvenient to give tablets, or patients cannot be trusted to take the tablets, then subcutaneous injections of a suspension of dapsone can be given subcutaneously or intramuscularly. The drug is made up as a suspension in groundnut or coconut oil with a small amount of antiseptic (phenol 0.5 per cent) sterilized, preferably by hot-air oven sterilization, and put into rubber-capped bottles. A convenient suspension contains 20 per cent of the drug. It has been found satisfactory to give weekly injections commencing at a dosage of 100 milligrams per week and increasing by 100 milligrams monthly up to 500 milligrams per week. Some authorities recommend fortnightly and others twice weekly injections. If given twice weekly the commencing dose is 50 milligrams rising by 50 milligrams each fortnight until 400 milligrams twice a week are given.

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The chief drawbacks of Promin therapy are three (*a*) It necessitates intravenous injections (*b*) it is expensive and (*c*) it has to be given under careful medical supervision When expense is not a serious factor then admittedly the intravenous route if carefully supervised is likely to give less difficulty than the intramuscular or subcutaneous routes and less pain. The dosages that were recommended by the Committee on Therapy at the International Leprosy Congress held at Havana in 1948 were as follows

In adult patients in good general condition and with a normal blood picture, an initial dose of 2 grammes in 5 millilitres of solution is given intravenously daily This dose should be increased after 1–2 weeks by 1 millilitre daily until a dose of 12 5 millilitres is reached The dosage for children depends on age, weight, general physique and individual tolerance. The drug should be administered daily for from 1 to 3 months followed by a rest period of from 1 to 2 weeks, after which treatment is resumed The dosage and the length of the rest periods may be modified in accordance with the requirements of the individual patient

Other chemotherapeutic and antibiotic agents in use in leprosy

It can be expected that a large number of such agents have been tried from time to time, but only the following merit consideration

Thiosemicarbazone

Ryrie (1950) Schujman (1950) and Dhamendra and Chatterjee (1952) have reported good results with thiosemicarbazone in leprosy but Lowe (1952) and Cochrane (1951) have expressed the opinion that these drugs are less efficient than the sulphones and should only be used in cases of intolerance to sulphone therapy In such cases a change to thiosemicarbazone for from 6 months to a year may be helpful in tiding over the reaction phases. The dosages recommended are 25 milligrams daily increasing each week by 25 milligrams until 150 milligrams per day is reached. Children of 12 years of age and under receive half this dose.

Lowe (1952) reported 6 cases of agranulocytosis under thiosemicarbazone, and Jopling (Jopling and Kirwan 1952) one case of toxic amblyopia.

We feel that the thiosemicarbazones have not given sufficient evidence of their superiority over other remedies to warrant their consideration in the routine treatment of leprosy and should only be used in cases markedly intolerant to the sulphones

Streptomycin

Erickson (1950) reported that streptomycin and dihydrostreptomycin appeared to have a superficial effect upon lesions of leprosy but concluded that in view of the toxicity of these preparations continuous administration was not advisable. Therefore, it is not possible to tell whether or not the drugs are capable of stopping the multiplication of *Myco leprae* in the tissues. Streptomycin, however may be tried in cases which are not responding satisfactorily A recommended course is a 6-week course giving 1 gramme daily followed by 3 months rest, then the course is repeated If definite improvement has not set in by the third course, then it is suggested the drug should be abandoned.

Isonicotinic acid hydrazide

This drug, which has been hailed as the most effective drug in the treatment of tuberculosis, and has now been shown to have its decided limitations, has been given a limited trial in leprosy. Lowe (1953) has reported unfavourably in a trial of 27 weeks duration, and experience in the use of this drug in cases in Great Britain has been disappointing. Some cases have shown clinical improvement but no bacteriological change over a period of 9 weeks. Current (unpublished communication) reports that, over a period of 6 months, 20 cases showed no clinical change, 1 case improved and 21 exhibited no bacteriological improvement. The one case that improved was found, subsequently to have had previous sulphone therapy. Whether combined therapy will be more successful remains to be seen, but all cases except one treated in Great Britain had previously received combined therapy.

The results of treatment with isonicotinic acid hydrazide are particularly disappointing, particularly as Barnett and Bushby (1953) reported that isonicotinic acid hydrazide in rat leprosy was superior to the sulphones. Robson (1953) has also reported favourable results in the corneae of mice infected with *Myco. lepraemurium* and treated with isonicotinic acid hydrazide, but states (personal communication) that improvement, which is at first slow and then rapid, only occurs after 6–8 weeks, and is not striking until the third month. This period in the human would be equivalent to 3–5 years. This emphasizes that conclusions as to results in infections of *Myco. lepraemurium* may not be comparable in human leprosy.

It should be pointed out that clinical results in leprosy may be unreliable and, therefore should be combined with adequate bacteriological examination and biopsies of the lesions taken, at least, at 6-monthly intervals.

Results of treatment

Tuberculoid cases

There has been a considerable discussion with reference to the results of treatment in tuberculoid leprosy. There is no doubt that all cases of tuberculoid leprosy will ultimately clear up under sulphone therapy when the percentage of resolutions is frequently in direct proportion to the severity of reaction. It is well known that the markedly active tuberculoid lesions tend spontaneously to heal, and fairly commonly suphone therapy stimulates further tissue reaction in the early phases and hastens the resolution of the disease. It is also well known that after a tuberculoid lesion has subsided residual hypo-pigmentation frequently is left, which may respond to the older methods of intradermal injection. If this method is not feasible, or is too painful, then other forms of counter-irritation—for example, painting the lesions with trichloracetic acid—may help in the repigmentation of lesions. It is advisable to use this acid cautiously.

Lepromatous cases

It is generally held that the results in lepromatous cases is highly satisfactory and this is usually the case. It must be remembered, however that a lepromatous case seldom becomes negative in less than years, and may require 5 years or more. Clinical results in the advanced lepromatous case are often dramatic (see Fig. 31) but bacteriological results may be disappointing. This case had been

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under treatment for 5 years and still an appreciable number of bacilli could be demonstrated in routine examinations. Admittedly after 5 years the infectivity of such cases is so often so markedly reduced that they can be considered of very little public health danger Nevertheless, this relative slowness of bacteriological results is causing a number of workers serious concern

Dimorphous lesions

In so far as these cases are liable to show gross tissue destruction and serious damage to nerves if they go into reaction great care must be taken whenever there is a likelihood of the diagnosis being a dimorphous case. Therefore, when in doubt it is always better to withhold treatment until the reaction has subsided.

Indeterminate lesions

It is always difficult to decide in lesions which appear to be inactive, whether treatment should be given A general rule is when in doubt the patient should be given the benefit of that doubt and be treated

Action of chemotherapeutic agents, with reference to the sulphones

There has been much discussion concerning the action of sulphone drugs, but most authorities accept the theory that they have a bacteriostatic effect on *Myco leprae* and their action therefore, should be studied in both lepromatous and tuberculoid leprosy

Lepromatous leprosy

A study of the histopathological material and examination of direct smears from lepromatous cases shows that the first changes which take place are in the morphology of *Myco leprae* These changes have been noted for many years and occur both in treated and untreated cases they have been seen by many workers in cases treated with hydnocarpus (chaulmoogra) oil and its derivatives. Under the sulphones however this phenomenon is noticed to a marked degree. The author has seen significant fragmentation of the acid-fast rods of *Myco leprae* take place within 20 days, and with a dose as low as 500 milligrams per week of the parent sulphone In some patients, particularly those sensitive to sulphone therapy this change is accompanied by a period of reaction which is different from that known as erythema nodosum leprosum Instead of the erythema nodosum type of lesion being the characteristic one, the patient shows numerous subcutaneous nodules accompanied by high fever These nodules frequently seem to coalesce and the skin—particularly of the forearms and thighs—is leathery to the touch The nodules in the dermis become fixed and suppurate, and in the small bead of pus which is extruded there are enormous numbers of bacilli many in globus formation This phenomenon unlike erythema nodosum may not be a favourable one and sulphone therapy must either be continued very carefully or suspended altogether This apparent ability of the sulphones to produce a reactivation of the disease will be referred to when we consider the actions of sulphones in tuberculoid cases

It appears therefore, to be correct that in some way or other the sulphones interfere with the metabolism of the organism and when this happens fragmented and granular forms of *Myco leprae* are noted If biopsies are made at various

stages in sulphone therapy particularly in the advanced stage, changes are seen in the globi. There, large bacillary masses are seen as if the bacilli are disappearing from within, and frequently a space appears to be left with bacilli in the granular form clinging around the periphery of the globus, or perhaps around a macrophage cell. (Whether a globus is a phase in the life history of the bacillus, or bacilli packed within a macrophage cell, is a matter of controversy.) When the bacilli show marked morphological changes the granulomatous infiltration in the dermis begins gradually to clear. It is interesting to note that as *Myco. leprae* become reduced in numbers, the infiltration in the dermis in the advanced cases, particularly the foamy cells, is not reduced proportionately and a stage comes, which has also been noted by other workers, when in the dermis there are areas of foamy cell-degeneration in which there are few or no bacilli. The granulomatous infiltration gradually disappears and the histology returns to the prelepromatous



FIG. 30.—The resolution of reactional major tuberculoid lesion. The patient had no treatment. The reaction occurred spontaneously and was severe and it is to be noted that at the end of 3 weeks the lesion had completely resolved leaving residual scarring and damage to the left facial nerve (lagophthalmos).

or uncharacteristic stage, showing slight round-cell infiltration in the dermis but in the nerves, which can usually be clearly seen, frequently bacillary granules or bacillary debris remain. The proportion of cases in which this is seen cannot be stated, but I have seen this phenomenon 18 months after the patient has become negative by standard methods of examination, in spite of the fact that adequate doses of the parent sulphone had been continued throughout this period.

It may be that the nerves act as "reservoirs" of the bacilli from which the disease can recrudesce. Khanolkar (1951) has described how in early lesions of pre-lepromatous leprosy *Myco. leprae* burst out of the subcutaneous nerves into the depth of the dermis, and gradually extend and multiply throughout the corium of the skin. The sulphones may therefore prepare the bacillus for more adequate phagocytosis and destruction of the macrophage cells, and thus enable, what seldom can be done under natural conditions, the macrophage cells to dispose of the granular forms of the bacillus. The complete bacteriological cure of an individual may depend on how successful this process is, and therefore it may be necessary

to continue maintenance doses of sulphones for prolonged periods, if not throughout life It is well to remind ourselves that clinical improvement in leprosy is far ahead of bacteriological improvement and therefore inadequate sulphone therapy or discontinuance of treatment, may result in the creation of human pockets of bacilli from which the disease may recur in an area where leprosy control methods, which largely depend on sulphone therapy have greatly reduced the numbers of infective cases It is a sobering thought to realize that the development of a case of leprosy from the point of inoculation to a full-blown lepromatous case may take many years While we have in the sulphones the most potent remedies as yet discovered injudicious or inadequate mass therapy may result in a serious situation arising owing to relapses occurring possibly many years later



Fig 31 —Nodular leprosy showing improvement under sulphone therapy The clinical lesions almost disappeared after 8 months, but the patient was st ll bacteriologically positive.

This does not mean that sulphone therapy should not be used as a powerful adjuvant to preventive measures it does, however indicate that these possibilities should be borne in mind, and that we should not too readily assume that the acid fast granules are dead bacilli, or merely bacillary debris for there is little evidence so far for this contention Wishful thinking is a dangerous preoccupation in leprosy and until much more information is available it is better to assume the viability of the organisms in all stages, and the necessity for treatment so long as they can be demonstrated in the tissues

As long as sulphone therapy is being administered it appears as if the clinical signs remain inconspicuous or clear up It may be that the granular forms are resistant forms of *Myco leprae* but as yet there has been no evidence of relapse so long as patients are taking maintenance dosage. The author believes a dosage

of 200–300 milligrams of DDS or 1–2 millilitres of a 50 per cent aqueous solution of sulphetrone twice a week is sufficient for this purpose.

Tuberculoid leprosy

The satisfactory results of sulphone therapy in many tuberculoid cases are of great interest. I hope, in due course, to submit evidence that the sulphone preparations appear as would be expected, most successful in the stage when leprosy is advanced, and there are large numbers of acid-fast rods in the tissues. I have



FIG. 32.—Photomicrograph of advanced lepromatous leprosy showing fretting of the epidermis and numerous bacilli in the corium. Note the relatively free zone between the epidermis and the granulomatous infiltration characteristic of this type of leprosy. (*By courtesy of the Wellcome Foundation.*)



FIG. 33.—A section of same case shown in Fig. 32, two years later. Note the return of the rete pegs and the disappearance of the granulomatous infiltration—granular bacilli, however were found in the subcutaneous nerves. (*By courtesy of the University of Glasgow.*)

seen cases in which the bacteriologic index was 3–4 clear up within 2–3 years, whereas in other cases in which the index was 1 or even less than 1 at the end of a similar period the patient was still positive to standard methods of examination. It is possible that in these earlier cases the bacilli are not multiplying so actively in the tissues, and therefore these drugs have not the same effect. The response to sulphone therapy in tuberculoid cases, however appears to be in proportion to the possibility of causing the tuberculoid lesions to pass into a reactive phase. I am of opinion that in many instances if sulphone therapy does not show a reasonable response in less than 8 months in tuberculoid leprosy it is doubtful whether the result is significant, and probably intensive intradermal injections would

produce equally satisfactory results. Admittedly however sulphones are easier to administer and therefore are not *only justified on this score but are more certain* to ensure freedom from relapse I believe the sulphones act in the tuberculoid case by virtue of their ability in the early *stage of the disease to stimulate Myco lepræ* into activity and as a result a favourable tissue response is stimulated and resolution of the lesions therefore hastened. *It is this ability to produce a violent* tissue response which has to be carefully considered before sulphones are administered to the reactional tuberculoid case, particularly that *variety which is known* as the border line intermediate or atypical case.

Criteria of cure

It has always been difficult to adopt a definition of cure and to estimate the length of treatment necessary In the days when hydnocarpus (chaulmoogra) treatment was the routine method the practice in India was to give, 6 months after all signs of activity ceased a quiescent certificate An arrested certificate was not given until 2 years had passed after cessation of treatment. With the sulphones the practice has not as yet been standardized, but it is felt that the following would be acceptable.

Tuberculoid cases

Treatment in tuberculoid cases should continue for one year after all activity has ceased or for 18 months from the commencement of treatment whichever is longer

Lepromatous cases

Treatment should continue for at least one year preferably two after the person is negative by standard methods of examination

In these cases much depends on the technique and numbers of smears, and also on the competence of the technician Unless the more thorough biopsy smear technique of the Bombay workers is used when a small but deep wedge-shaped piece of skin is excised and the whole tissue smeared on several slides and carefully examined I am of opinion that at least 8 smears (excluding the nose) should be taken from the skin Once a patient is negative, smears should be *done monthly* during the first 6 months, 3-monthly for the next 6 months, and 6-monthly for a further year *Some authorities (Johansen 1951 and Cochrane, 1951) hold* that it is a wise precaution, when practicable, to continue a maintenance dose—half *the maximum dose, that is, 300–400 milligrams of DDS* per week—for life.

Reactions in leprosy

Because of the increase in the possibility of reactions under sulphone therapy it might be well to discuss these phenomena, which should be considered under the three separate categories of (*a*) violent local tissue response (*b*) erythema nodosum or acute lepra reaction and (*c*) subacute, or chronic, lepra reaction The first is seen in the leprides or tuberculoid cases. I believe that sulphones act in tuberculoid cases by virtue of the fact that they cause the bacilli, in the early stages, to multiply and this sets off the trigger which results in an acute tissue response Because of this reaction resolution of the disease is more rapid, and thus sulphones hasten the recovery of the patient. The speed of the recovery *is*

in direct proportion to the intensity of the reaction. It is because of this capacity to set up reactions in the leprides that care must be taken lest increased nerve damage is produced, with resultant severe deformity. It is, therefore, sometimes advisable to excise the nerve sheath, in those cases which show gross enlargement of the nerve with oedema and tenderness, before sulphone therapy is started.

The reaction in the leprides, and to some extent in the dimorphous lesions, is an acute antigen–antibody response seen locally in the tissues. Because of this localized response in tuberculoid leprosy some lesions may flare, while others are quiescent. In other words the antigen—the bacillary products—is localized in the tissue.

In the second form of reaction—erythema nodosum leprosum—the mechanism of the response is different and the approach to its control must be along other lines. This, too, is an allergic phenomenon, but the antigen—bacillary products—is no longer confined to the tissues, but is circulating as a result of the rapid multiplication of *Myco. leprae* and their equally rapid destruction, a hypersensitivity arises and high fever and erythema nodosum lesions are seen. The tissues themselves are not sensitized but there is a humoral response to the bacillary products—that is to say erythema nodosum is a type of Herxheimer reaction and comes under Stokes's definition of a toxi-lepid. In this connexion I quote from Stokes and his associates (1942)—"It is probable that the toxi erythemas, erythema multiforme as well as erythema nodosum in its various forms can be explained on an -id basis, associated with central, local or blood stream infection." The failure to understand the mechanism of these two different allergic phenomena gives rise to much confusion.

It is interesting to note that cortisone or ACTH in relatively small doses, 50 milligrams per day, appears to control erythema nodosum and permits the continuance of sulphone therapy. More recent information from Lowe (1952) in West Africa, however, suggests that this form of treatment should be of short duration, lest the disease itself be aggravated. In the true erythema nodosum phase, however, cortisone carefully administered can be of great help in tiding over the acute reaction.

The other form of reaction, in which there is rapid multiplication of *Myco. leprae* without corresponding destruction, is much more serious and indicates the necessity for the immediate cessation of sulphone therapy and its very gradual resumption when the acute phase has passed. Cortisone would be definitely contra-indicated in this phase of reaction.

Ancillary treatments

Whilst it does not come within the scope of this contribution, it should be mentioned that the success of modern therapy has greatly increased the opportunities for plastic and orthopaedic surgery. It may be said that there is not only a reasonable chance of a patient becoming clinically free of his disease and remaining so, but that adequate surgical measures can be taken to remedy or prevent the distressing deformities which are so often the end-results when the disease is allowed to run its course, or when less effective and more prolonged treatment has been undertaken. The work of Brand (1950) should be mentioned in this connexion. He states that "the first duty of the Medical Officer is to see that claw hand never develops" and that "a little careful application of the science and art of Ortho-

paedic Surgery may be able to change the outlook from one of hopelessness and despondency to one in which the patient can look forward to a life of usefulness and activity

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CHAPTER 10

THE PATHOGENESIS OF TINEA CAPITIS

R. W RIDDELL

INTRODUCTION

TINEA CAPITIS is caused by species of *Microsporum* and *Trichophyton*. *Epidermophyton*, the remaining genus of the dermatophytes (or ringworm fungi), does not attack hair *In vitro* the nutritive requirements of these fungi are not particularly exacting, but in keratinized tissues attached to the living human or animal host, they have a very restricted growth form. This consists merely of fungal filaments (hyphae) which segment into chains of cubical or rectangular spores (arthrospores). These spores may remain viable in living tissues when introduced experimentally but they germinate and produce invasive hyphae only in completely keratinized parts of *stratum corneum* nail-plates and hairs. If the infected material is removed from these hosts and placed under suitable conditions of temperature and humidity (preferably on a culture medium), a greater variety of structures is produced, some of them diagnostic of fungus genus or species. In the *stratum corneum*, *Microsporum* and *Trichophyton* species have an identical appearance, but during invasion of hair behaviour differences become apparent, particularly in arthrospore arrangement and production of fluorescent material. These properties have been summarized by Riddell (1951).

AGE AS FACTOR IN DEVELOPMENT OF TINEA CAPITIS

Scalp ringworm is predominantly a disease of children, particularly when due to *Microsporum audouini* and *M canis* At puberty regression of the infection usually occurs spontaneously even in untreated cases, suggesting that some protective factors then become operative. Rothman and his colleagues (1947) attempted to correlate the presence of fungicidal substances in post-pubertal sebum with this apparent immunity of the adult scalp Fungistatic activity against *M audouini* was estimated to be four times greater in adult sebum than in prepubertal hair fat. Saturated fatty acids, containing odd numbers of carbon atoms ranging from 7 to 13 were held to be responsible for this finding. Kligman and Ginsberg (1950), however ere unable to confirm these results. They suggested that the increased excretion of sebum after puberty might account in part for the rarity of adult ringworm. Other possible explanations are the presence of fungus-inhibiting substances within adult hair shafts, or a decline in concentration of growth factors with age.

FUNGUS SPECIES AS FACTOR IN SPORADIC AND EPIDEMIC INFECTIONS

Amongst children, tinea capitis is often an epidemic disease. In adults it is rare and always sporadic. *M audouini* and *M canis* are both frequent infective agents.

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About 60 per cent of inoculated children prove susceptible to scalp infection by these two species of *Microsporum*. A lesser proportion of adults become infected, and the lesions they produce are smaller and of shorter duration In the subjects whose scalps resist experimental infection by *M audouini* or *T mentagrophytes*, inoculation of glabrous skin with the same organism almost invariably produces the disease.

Early hair infection

Within the first week after infection by *M audouini* extracted hairs show a zone of bright, yellowish-green fluorescence under Wood's lamp. This zone occupies about one millimetre of the shaft close to the bulb of the hair root. The fluorescent band approaches the follicular orifice at the rate of 0 3 millimetre daily until it becomes visible at the scalp surface 12 days after the commencement of the infection. The fluorescent zone never encroaches upon the lower 0·75 millimetre of the shaft. After the tenth day an attempt to extract an infected hair results in fracture about 2 millimetres above the bulb

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Follicular infection.—Occasionally infection remains confined to scattered

The former an obligatory human pathogen, causes more extensive and persistent epidemics This difference cannot be entirely explained by the greater frequency of inflammatory reactions accompanying *M canis* infections In most cases, natural infections produced by these two fungi are clinically indistinguishable. The apparent immunity of the adult scalp cannot be attributed wholly to any intrinsic tissue resistance, since experimental disease with *M canis* may readily be produced

More localized outbreaks in schools and families result from *Trichophyton sulphureum* infections (Kligman and Constant 1951) *T violaceum* and *T schoenleini* are organisms of lower infectivity and usually require the more intimate contact of family life, or some degree of overcrowding and neglect. *T discoides*, the causative organism of cattle ringworm is highly infectious, and frequently responsible for suppurative ringworm in children and adults The infection is contracted directly from cattle or from fomites. *T mentagrophytes* may also produce sporadic disease

TISSUE REACTIONS IN RELATION TO FUNGUS SPECIES

In infections due to *M audouini* and *M canis* there is usually no more than slight hyperkeratosis and a moderate monocytic infiltration of the upper corium An inflammatory response is one of the mechanisms by which spontaneous cure is achieved (Scully Livingood and Pillsbury 1948) The possibility of some allergic reaction related to the regression of infection, has been suggested by the simultaneous development of cutaneous sensitivity to trichophytin

Tissue reactions of negligible degree also accompany infection by obligatory human pathogens such as *M audouini T sulphureum* and *T violaceum* the destructive lesions of favus (*T schoenleini* infection) being exceptional. On the other hand, acute inflammation often follows infection by species normally found on animals, notably *T discoides* and *T mentagrophytes*

EXPERIMENTAL INFECTIONS PRODUCED BY *MICROSPORUM* SPECIES

By their classical studies, Sabouraud in France, and Fox, Blaxall and Adamson in Great Britain, established the basic principles of the pathology of ringworm. Their work was done with manually extracted hairs. Kligman has recently advanced these studies at the University of Pennsylvania, using biopsy specimens taken at various intervals in natural and experimental infections in children and adults These contributions may lead to more effective methods of therapy Though part of this work has been reported in the literature (Kligman, 1952), much of the pathology here described represents previously unpublished work and is presented through the courtesy of Dr Kligman It should be stated that the inoculations were not performed at random on a normal community but on inmates of an institution in which tinea capitis was endemic. When the pathology in natural and experimental infections was compared no differences were noted.

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Follicular infection.—Occasionally infection remains confined to scattered

follicles and hairs at the inoculation site. As the disease becomes established these hairs fluoresce but those extracted from adjacent areas do not show basal fluorescence The surrounding *stratum corneum* is not invaded

Refractory period

When a circinate lesion attains its maximum size, the peripheral fluorescence test becomes negative The skin manifestations of infection disappear and the disease persists as a pure infection of hairs Equilibrium is thus reached in the host–parasite relationship This period is of variable length and satellite lesions rarely develop When they do they are small and resolve promptly During this period if examination under Wood s lamp is omitted the presence of disease is revealed only by slight scaling and broken hairs

Involution period

Spontaneous resolution usually occurs within 7 months, mostly without any inflammatory reaction to which it might be attributed

Experimental infections with *M canis* always produce circinate lesions confined to the site of inoculation, and involution begins when the lesions are smaller than those of *M audouini* Inflammation ranging from folliculitis to mild kerion, is seen more frequently than is usual in natural infections, with this organism. Resolution occurs within 5 or even 3 months.

Pathology of tinea capitis

In these experiments spores from naturally infected hairs were used for inoculations, so it could be assumed that the presence of hyphae in biopsy material of the scalp signified the establishment of infection

Infection of stratum corneum

Where infection of the *stratum corneum* occurs, hyphae as well as inoculated spores may be found in the outer layers of keratin on the second or third day Germination and growth is, therefore, as rapid *in vivo* as *in vitro* Circinate lesions show numerous hyphae in the spreading edges, but few in the centre, as is usual in tinea circinata of glabrous skin Once the refractory period begins, hyphae disappear from the scalp in a matter of weeks and the fungus remains only in the follicles

Follicular infection

Follicular infection is essentially the same in all ringworm infections of the scalp due to species of *Microsporum* or *Trichophyton* and it may occur irrespective of the presence in the follicle of a susceptible hair By the third day following inoculation with *M audouini* spores, a mass of hyphae accumulates at the follicular orifice, forming the mycotic cone described by Sabouraud (Fig 34 (*a*)). (Kligman draws attention to the close proximity of this mycelial mass to sebum-excreting glands and suggests that fungistatic powers of sebum are inadequate *in vivo*) These hyphae soon segment into chains of arthrospores which form groups of large polymorphic cells of various sizes (Fig 34 (*b*)) Some large hyphal segments may also be seen, corresponding to the "giant hyphae" of Fox and Blaxall or the ghost hyphae" of Sabouraud

The fungus leaves the *stratum corneum* of the scalp and enters the potential space between the hair shaft and the tightly organized concentric lamellae of keratin produced by the external root sheath cells. Contrary to Sabouraud's belief this dense keratin and the more loosely organized meshwork of keratin



FIG. 34 Experimental *M. audouini* infection (human) Sections of biopsy materials taken on 4th day of disease (Periodic acid Schiff stain) (a) Oblique section showing accumulation of hyphae around hair shaft in follicular orifice (b) Longitudinal section showing the lumen of the follicle filled with large polymorphic cells (arthrospores) of various sizes.

beneath it are not invaded (Fig. 35) Below the level of the sebaceous glands and 0.75 millimetre below the follicle mouth the descending hyphae come into contact with, and grow over the hy alinized cells lining the external root sheath. These are about three layers deep and are derived from the internal root sheath cells a little above the level of the papilla. As they are produced, these cells slide upwards over the surface of the external root sheath, finally to desquamate in the region of the sebaceous glands They may be displaced by fungous growth but not invaded. The hyphae entwine the hair shaft as they descend the follicle, proliferating on its surface, and breaking up into arthrospores which are readily disorientated ("primary spore formation"). This downward growth ceases by about the tenth day at approximately 1 millimetre above the tip of the hair papilla. In

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this region, the hyphae are younger and of smaller diameter than filaments further from the papilla.

Hair infection

Invasion of susceptible hair begins on the sixth day or later coincident with the earliest appearance of fluorescent material. Fluorescence is not seen in the abundant hyphae and arthrospores present around the hair before invasion takes place. Hyphae penetrate the hairs about 0·5 millimetre either side of the mid-point of their intrafollicular portions. As illustrated by Sabouraud, the fungus penetrates under the cuticle cells and then grows downwards in the subcuticular portion of the cortex, forming arthrospores and stripping off the cuticle (Fig 36). Some penetrate more deeply into the cortex, branching repeatedly in their downward growth towards the bulb and reaching their terminal position about the tenth day These hyphae tend to form long cells with infrequent septations. The deeper hyphae are narrower and more deeply staining than the older portions present distally in the hair

The fungous filaments, both within and about the hair have thus descended in parallel as more or less separate systems to reach the lower limits by the tenth day

The lowest limit of the downward-growing intrapilary hyphae is known as Adamson's fringe. Adamson (1895) thought this lay external to the hair and beneath the spore sheath, but Sabouraud recognized its true position. The fringe lies at the upper limit of the keratogenous zone of cells which occupies about 0 75 1 5 millimetre of the lowest portion of the hair shaft, above the point where it merges with the matrix cells of the bulb As they travel away from the papilla, these cells become progressively more fusiform and their cytoplasm more fibrillary By the time they reach the upper limit of the keratogenous zone their cell walls and nuclei are no longer apparent, and their cytoplasm has been converted into a dense mass of fibrils. It is along the grain of these keratinized fibrils that the fungus descends, but it is abruptly halted at the inverted v-shaped upper limit of the keratogenous zone. At this level the fusiform cells, though almost completely keratinized, are still faintly nucleated (Fig. 37).

The host parasite relationship is now perfected provided that inflammatory changes do not ensue The keratinized shaft is invaded by fungus as soon as it is being formed at the upper limit of the keratogenous zone, that is at the rate of about 0 3 millimetre daily If keratinization took place more rapidly than fungous invasion, the infecting organism would be pushed to the surface and eliminated.

The growing hair carries the fungus with it to the scalp surface, and for some distance beyond The hyphae which penetrate the hair in the mid-portion of the follicle reach the surface on about the twelfth day Weakening of the shaft in *Microsporum* infections causes natural fracture of the hairs a few millimetres above the scalp Even gentle pulling usually breaks the hair within the follicle at a point some millimetres above the bulb, but the infection always persists in the shaft below the line of rupture But for the supporting walls of the follicle, fracture would occur even closer to the hair root.

In *T violaceum* and other endothrix infections causing natural hair fracture at the follicle mouth, the intrafollicular portion of hair may be almost entirely replaced by a soft mass of spores and is best removed for examination by scooping out with a fine probe.



FIG 35.—Experimental *M. audouini* infection (human). Oblique section showing early follicular invasion. Hyphae growing down keratin tube between hair shaft and lamellae of keratin covering external root sheath cells. (Periodic acid Schiff stain.)



FIG 36.—Experimental *M. audouini* fection (human). Longitudinal section of biopsy material taken on 5th day of disease. Hyphae are segmented and have penetrated under cuticle of the hair. (Periodic acid Schiff stain.)

man has demonstrated how this occurs. A zone of "provisional spore formation" develops just above Adamson's fringe by the emergence from the hair of interwined hyphae with short twisting lateral branches (Figs. 38 and 39). Septation occurs very rapidly in the dense entanglement of external mycelium, resulting in chains of arthrospores which are so short and curved that any linear arrangement is obscured in the mosaic like mass of cells. The spores vary in size and are

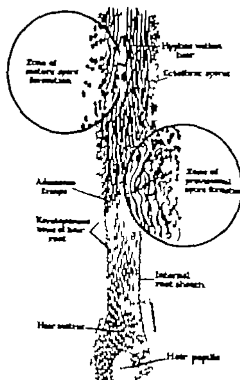


Fig. 38.—Diagram to illustrate the mode of formation of ectothrix spores in *M. audouini* infection.

Fig. 39.—Experimental *M. audouini* infection (human). Oblique section near base of hair where provisional spores are forming. Intrapilary hyphae form a dense mass and short reflexed branches are produced as hair surface is reached. (Periodic acid Schiff stain.)



cuboidal or rectangular with facetted sides. Derived as they are from younger mycelium, they are smaller than intrapilary spores and stain more avidly. This zone is about 0·25–0·5 millimetre in width and takes about a day to develop. As it is carried up the follicle by the growing hair it becomes a zone of "mature spore formation." Here the chains of spores are dissociated into separated spherical cells. These are carried to the surface with the growing hair which they ensheath. At this level, the hair itself contains only a few filaments of degenerating hyphae (Figs. 40 and 41).

The ectothrix spores in *Trichophyton* infections are arthrospores of external hyphae and are not formed in the manner just described. They are originally produced from more or less straight filaments coursing along the hair and they tend to retain their linear form.

In favus the hair shaft is irregularly tunnelled by hyphae which weaken it less than the infections already considered. Consequently long lengths of infected hair are carried beyond the follicle mouths by the growth of the hair and are seen to fluoresce a dull greenish colour under Wood's lamp. The associated follicular damage results in a cup-like depression filled with a yellowish scutulum, consisting of hyphae and spores. The hair papilla itself may be destroyed by this process.

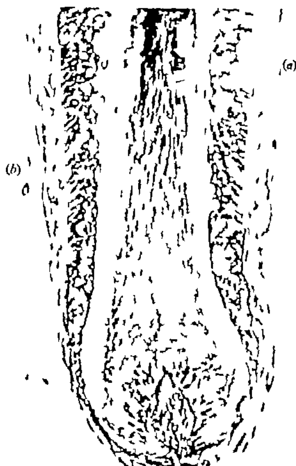


FIG 37.—Experimental *M. audouini* infection (human). Longitudinal section of biopsy material showing mature infection. Relationship of Adamson's fringe to normal structures is demonstrated. (Periodic acid Schiff stain.) (a) Adamson's fringe (b) keratogenous zone.

Degeneration of hyphae in these long lengths of infected hair become so marked that they are typically replaced by elongated air spaces.

Regression of extrapilary hyphae and development of "zones of provisional and mature spore formation

At about the time of formation of Adamson's fringe extrapilary hyphae regress, and primary spore formation ceases. In the case of fungi that produce endothrix infections, there is no further development of fungous mycelium outside the hair. In *Microsporum* infections, however, intrapilary hyphae emerge through the hair surface, giving rise to ectothrix spores peculiar to infections by this genus. Klig

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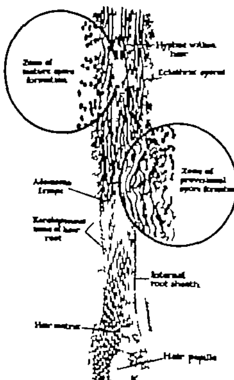


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The ectothrix spores in *Trichophyton* infections are arthrospores of external hyphae and are not formed in the manner just described. They are originally produced from more or less straight filaments coursing along the hair and they tend to retain their linear form.



FIG. 40.—Experimental *M. audouini* infection (human). Longitudinal section of biopsy material from mature infection. Near scalp surface intrapilary hyphae have degenerated, and integrity of hair at this level is almost lost. (Periodic acid Schiff stain.)

FIG. 41.—Natural *M. canis* infection (cat). Transverse section to show small-spored ectothrix infection. (Periodic acid Schiff stain.)

Stage of involution

A progressive diminution in the quantity of intrapilary hyphae finally occurs, together with an inhibition of spore formation. In the last stages of infection no further ectothrix spores are produced, and only a few filaments remain in the hair. Diminished fluorescence coincides with this decrease in intrapilary hyphae.

FACTORS DETERMINING PERSISTENCE OF INFECTION

A mature patch of ringworm becomes a series of independent infections of hairs at different stages in their life-cycles. Though follicles appear to be uniformly vulnerable, their contained hairs vary in susceptibility the reasons for which are uncertain. Further involution of infection in some hairs is delayed long after the great majority have become normal.

The downward growth of hyphae towards the hair bulb appears to be due to the influence of chemotactic substances. Kligman suggests that the inhibition of fungus at the upper border of the keratogenous zone may be due to the presence of an inhibitor substance, possibly concentrated there by the rapid dehydration which occurs in these cells. Alternatively some subtle chemical differences may determine the issue. The hair keratin is consolidated above the keratogenous zone and its contained sulphur exists in the form of sulphydryl groups, whereas the unconsolidated keratin in the zone itself contains sulphur in the form of disulphide linkages.

There are two ways in which natural termination of infection may occur. The first is at the stage of formation of a club hair or resting hair. Apart from rare infections which persist for years this phenomenon is unimportant in terminating infection of scalp hairs which have a long life-cycle. It is, however, effective, in shortening infections of cilia of eyelids and hairs of glabrous skin. As a club hair develops, spore formation stops entirely and intrapilary hyphae disappear except possibly for a few strands. It is noteworthy that these hairs are no longer susceptible to extensive invasion, and are equivalent to hairs removed from their follicles. This change in susceptibility may be due to a diminution in growth-factors derived from the protoplasm of the hair matrix cells during declining hair-growth. There is a similar absence of intrapilary growth in an extracted hair inoculated with fungi capable of causing *tinea capitis*: an abundant growth occurs around the hair associated with only insignificant penetration of its substance.

The second method of natural termination is the development of an acute inflammatory reaction. This leads to a collapse of the follicle and to arrest of keratin production.

Artificial interference with the course of infection may take the form of application of irritant substances to incite an inflammatory reaction, or exposure to x-rays which inhibit keratin formation.

Effective antifungal therapy necessitates the termination of the relationship existing at the level of Adamson's fringe where keratin is invaded immediately it is formed. If this could be achieved, the fungus colony within the follicle would die. Destruction of the rest of the hyphae and spores is successful only in preventing transmission of disease. It is difficult to achieve adequate penetration of follicles by fungistatic agents, which are therefore, not brought into contact with

infecting fungi Those agents at present in use do not cure tinea capitis due to *M audouini* a disease requiring x ray therapy They may however help to hasten cure in scalp infections caused by dermatophytes inciting inflammatory reactions.

ACKNOWLEDGMENTS

Figures 34 to 40 are presented by courtesy of Dr A. M Kligman, Department of Dermatology and Syphilology University of Pennsylvania School of Medicine

Figure 41 is shown through the kindness of the Department of Pathology King s College Hospital Medical School London

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CHAPTER 11

SOME CURRENT PROBLEMS IN CUTANEOUS BACTERIOLOGY

D. M. PILLSBURY AND A. M. KLIGMAN

THE NEED for a more precise understanding of the factors which maintain the skin in a condition of health by reason of its ability to fend off pathogenic bacteria has not been lessened by the increasing availability of a wide variety of anti-bacterial agents. While the treatment of acute bacterial infections of the skin has been rendered much more effective through these agents, they are often disappointing when used in conditions in which chronic bacterial infection seems a principal factor. Moreover this unexpected lack of efficiency has demonstrated that the role of bacteria in some dermatoses may have been over-emphasized, and that other aetiologic factors are more important. For these reasons it has seemed worth while to summarize briefly some of the older data in regard to the bacterial flora of normal and abnormal skin and to attempt to correlate the findings reported in some more recent studies. Included in this critical review are some as yet unpublished studies from our own laboratories. We shall deal particularly with (1) the "normal" skin flora especially in regard to its variation at different sites on the skin surface, and between different individuals (2) the chief sites of localization of bacteria on and within the skin (3) the numbers of bacteria present on the skin (4) the criteria to be used in determining whether or not presumably pathogenic organisms found on the skin are causing disease (5) newer data relative to the mechanisms by which the skin "degerms" itself and (6) certain hypotheses in regard to allergic sensitivity to bacteria as a factor in promoting diseases of the skin. It will be immediately apparent to the reader that there are considerable gaps in our knowledge of the bacterial ecology and immunology of the skin, and we propose to point these out clearly to indicate the need for continuance of studies of a fundamental nature in this field.

THE FLORA OF THE NORMAL SKIN

The skin is never sterile and cannot be rendered so by any practical means. A variety of nitrogenous and lipoid constituents enable it to support a luxuriant microflora on its surface and in the orifices of its specialized glands. This is predominantly bacterial. A diversity of organisms has been isolated and studies by various investigators have yielded variable findings (Evans and his colleagues, 1950 Mayer and Spector 1932 Pillsbury and Nichols, 1946). Individual variability in the flora of different persons is perhaps a characteristic feature. Conditions of the environment, upper respiratory infection, and sweating are among the many factors which influence the skin flora both qualitatively and quantitatively. For this reason it may not be either wise or possible to attempt any strict

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designation of various bacteria as being parts of the "normal" or "abnormal" flora of the skin

Variations in technical methods undoubtedly account for some of the conflicting reports by various investigators The methods which have been applied for sampling the cutaneous microflora include (1) swabbing and scraping (Evans and his colleagues 1950) (2) surgical scrubbing of the hands and forearms with soap and water (Price 1938) (3) standardized scrubbing of small areas with a mechanically rotated brush (Rebell and his colleagues, 1950) and (4) skin biopsies (Rebell and Pillsbury unpublished) As is well known the Price technique employs a series of one minute scrubs of the hands and forearms with soap and water with determination of the number of bacterial colonies grown from samples of successive rinsings. When the scrubbing is done by trained subjects, this offers a convenient method of sampling the bacteria on a relatively large surface of the skin, with reasonable accuracy On the other hand Rebell and Pillsbury (unpublished) show that with this method some 90 per cent of the bacteria obtained come from the hand and this may represent an exceedingly variable flora because of the constant contamination of the hands from outside sources In interpreting the various studies which have been done using this method and modifications of it, it should be kept in mind that the bacterial flora will not be the same over all the skin surface. There are many specialized areas such as the ear canals the palms, the axillae and intertriginous regions in which the skin varies quite markedly both anatomically and physiologically

It is quite surprising that until recently those who have studied the cutaneous microflora have not included suitable anaerobic methods of culture routinely That this was a considerable oversight is seen from Evans (1950) demonstration of the great preponderance of anaerobic organisms on the unspecialized glabrous skin Another technical source of variation results from the tendency of certain organisms to form small colonies in culture These are crowded out by more rapidly growing organisms This is one of the reasons, for instance, why certain aerobic lipophilic diphtheroids have often not been recognized as part of the bacterial flora of normal skin (Pollock Wainwright and Manson, 1949) It is necessary to use appropriate dilutions of the sample, and to incubate cultures both aerobically and anaerobically on favourable media to overcome some of these limitations

A great many kinds of bacteria may be recovered from the normal skin, particularly if multiple samples are taken repeatedly from different areas Organisms from the gastro-intestinal genito-urinary and respiratory tracts are constantly being deposited on the skin Many external sources provide continuous contamination This may explain why for instance, different investigators have reported the recovery of coagulase positive *Staphylococcus aureus* with varying frequency (Gillespie Devenish and Cowan 1939 Miles Williams and Clayton Cooper 1944) Williams (1946) was able to recover this organism from the skin of 70 per cent of normal subjects while Pillsbury and Nichols (1946), using the Price technique, did not find this organism frequently on the hands of their subjects Price (1938) has contributed a very useful concept in distinguishing between the resident and transient microflora The resident flora includes organisms which are found more or less regularly in appreciable numbers on the skin of normal individuals These organisms represent stable communities on the surface of

the skin which are not easily dislodged. The precise ecologic forces which enable these resident organisms to maintain themselves without allowing intrusion of contaminant organisms into the population are not well known. Organisms which are indubitably pathogenic are not ordinarily part of the resident flora.

The transient bacteria include a diversity of organisms which do not maintain themselves indefinitely on the normal skin. These bacteria are more readily removed by scrubbing and other means. Both pathogenic and non-pathogenic organisms may be transient. In a general way the variety of transients will depend on the degree and quality of exposure to contamination. Price (1938) found that he acquired a transient flora of streptococci and Gram-negative rods when he was in daily attendance on patients with infected gunshot wounds. In the same way coagulase-positive staphylococci are often present among the normal skin organisms of individuals with carbuncles and furuncles, or with chronic foci of the organisms in the upper respiratory tract. Under these circumstances a transient organism may persist on the skin for fairly long periods, but only as a rule, when there is continuous replenishment from some external or internal source.

A complete list of the transient organisms would include essentially all the microbial species found in the environment of man. The most common transients are various staphylococci and streptococci, Gram-negative rods from the gastro-intestinal tract, diphtheroids, *Sarcina* and Gram-positive spore formers. Species of *Candida* and *Cryptococcus* are among the commoner fungus transients (Ravits, 1949 Marwin 1949), though they are rarely found in appreciable number unless, in the case of *Candida* the patient has been receiving one of the broad-spectrum antibiotics (Kligman, 1952). It is doubtful whether the common fungus saprophytes, such as *Aspergillus* and *Penicillium*, can grow or reproduce even temporarily on the normal glabrous skin surface. However these weed moulds are found not infrequently in cultures from the normal skin.

With these limitations in mind, the present knowledge concerning the flora of the normal skin may be summarized according to the scheme given below. This scheme is arbitrary in that certain organisms are listed as part of the resident flora, but this may be true for some subjects but not for others. For the most part, however the species listed are found in abundance on the skin of many normal persons. It is to be emphasized that this flora may not be characteristic of all regions of the body

The following species are those which are frequently encountered on the non-specialized glabrous skin

I. Aerobic Flora

A. Bacteria

1. Micrococci (Staphylococci)
   - *M. epidermidis*
   - *M. albus*
   - *M. candidus*
   - *M. flavus*
2. Corynebacteria
   - Lipophilic Corynebacterium
   - (Corynebacterium known in the [illegible])

B. Lipophilic fungi

1. Pityrosporon
   - *P. ovale*
   - *P. orbiculare*

II. Anaerobic Flora

A. *Propionibacterium acnes*

B. *M. saccharolyticus*

designation of various bacteria as being parts of the "normal" or "abnormal" flora of the skin

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- *M albus*
- *M candidus*
- *M flavus*

2 Corynebacteria
- Lipophilic *Corynebacterium*
- (*Corynebacterium acnes* in the adult)

B. Lipophilic fungi
1 Pityrosporon
- *P ovale*
- *P orbiculare*

II ANAEROBIC FLORA

A *Propionibacterium acnes*
B *M saccharolyticus*

The recent studies by Evans (1950) and to a less extent, those of Pillsbury and Rebell (1952) have enlarged our knowledge of the flora of the normal skin The aerobic bacterial flora is made up primarily of micrococci (staphylococci). *M epidermis* and *M albus* are most common *M candidus* and *M flavus* are common on some skins and absent on others Bergey's (1948) most recent designation of what was previously called *Staphylococcus albus* is *M pyogenes* var *albus* The pathogenic organism previously called *Staphylococcus aureus* now has taxonomic status as *M pyogenes* var *aureus* This emphasizes the close relationship between these organisms They cannot be separated reliably on the basis of colony colour The coagulase test provides the best criterion for distinguishing the pathogenic staphylococcus from its less virulent relative (Much 1908) Other properties usually but not always, associated with *M pyogenes* var *aureus* are orange colour haemolysis mannitol fermentation and pathogenicity for rabbit (Chapman *et al.*, 1938) On the other hand one must recognize that coagulase negative staphylococci may be haemolytic, may have an orange colour and may ferment mannitol resembling the virulent variety in all these respects (Rebell 1947) Indeed the acquisition of pathogenicity by *Staphylococcus albus* under appropriate circumstances may be possible Rebell (1947) has isolated this organism in pure culture from furuncles and from folliculitis, lesions which ordinarily yield coagulase positive *Staphylococcus aureus* Likewise, one cannot always assume that *M pyogenes* var *albus* is an innocent secondary invader although for the most part the pathogenicity of this organism is not great enough to be consequential

Pollock and Wainwright (1949) have demonstrated the presence of an oleic acid requiring species of *Corynebacterium* on the normal human skin. Rebell and Pillsbury (unpublished) consider this organism to be identical with *Corynebacterium xerose* The skin with its rich mantle of sebaceous material is ideally suited for lipoid-dependent strains of bacteria and fungi Oleic acid is an important constituent of sebum (Ricketts and his colleagues 1951) It is of more than passing interest, then that this acid has been found necessary or at least stimulatory to the growth of a number of normal skin residents (*Corynebacterium* (Pollock Wainwright and Manson 1949) *Propionibacterium* (Pillsbury and Rebell 1952) and *Pityrosporon* (Benham, 1941)) Crissey Rebell and Laskas (1952) have isolated another *Corynebacterium* species (*C tenuis*) from normal axillary hairs, as well as from persons with so-called trichomycosis axillaris. This organism is regularly associated with trichomycosis axillaris but was considered by these writers not to be a fungus The fungous aetiology of this condition is thus in doubt. This organism has a distinct preference for an alkaline *pH* and presumably should be considered part of the normal flora adapted to this region It is distinct from the oleic-acid requiring *Corynebacterium* of the glabrous skin

The so-called bottle bacillus *Pityrosporon ovale* is in reality a yeast-like fungus which reproduces by budding. It is found abundantly on sebaceous areas such as the face and scalp It may often be seen in smears of comedones. Being lipoid dependent, its existence in areas richly supplied with sebaceous glands is explicable. There is no real evidence however that this organism causes dandruff or seborrhoeic dermatitis.

Pityrosporon orbiculare has been isolated from lesions of tinea versicolor as well as from normal skin by Gordon (1951) The round budding cells of *P orbiculare* which are not infrequently seen in scrapings from glabrous skin

cannot in our opinion be distinguished from those which make up the grape like clusters in tinea versicolor. There is, in our opinion, the possibility that, in a susceptible individual *P. orbiculare* may acquire pathogenicity and thus cause tinea versicolor. This hypothesis requires that the organism in its pathogenic phase should have the capacity to produce hyphal segments, in addition to yeast like cells. An analogy with *Candida albicans* comes immediately to mind. When this latter organism is part of the normal mouth flora, its morphology is that of a budding yeast. Filaments and budding cells are found together in the pathogenic state, as for instance when a specimen from a case of thrush is examined. Perhaps

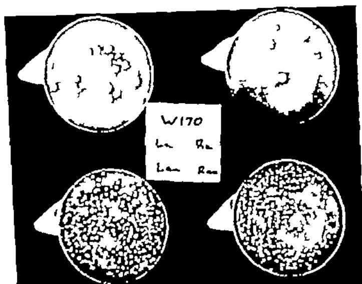


FIG. 42.—The bacterial flora of the normal human skin. Aluminium plates containing an agar medium were placed in contact with the skin and subsequently incubated aerobically or anaerobically. Note the marked predominance of anaerobes. La—Left arm, aerobic incubation. Ra—Right arm, aerobic incubation. Lan—Left arm, anaerobic incubation. Ran—Right arm, anaerobic incubation. (*By courtesy of J. Invest. Dermat.*)

the notorious persistence of tinea versicolor may be ascribed to the unrestrained growth of a normal skin fungus in a particularly susceptible individual.

Evans (1950) recent quantitative work on the anaerobic skin flora has shown that the anaerobic bacteria outnumber the aerobic by 10–100 times (Fig. 42). Evans has shown beyond doubt that these organisms are associated with areas rich in sebaceous glands, although we doubt that his data permit the conclusion that the glands themselves are the normal habitat of this organism. Unna first saw this bacillus in smears from comedones (Evans and his colleagues 1950). Sabouraud (1897) later cultured it from acne pustules. It enjoyed the distinctive name of the acne bacillus and was thought to be the cause of acne vulgaris. Its causal relationship to this disease is unproved. The organism resembles a diphtheroid and has gone under the name of *Corynebacterium acnes* until recently. Lovejoy and Hastings (1911) were able to isolate it from normal skin for the first time in

1911 It is remarkable that it is only since the work of Evans (1950) that its numerical predominance on the skin has been appreciated. This is partly due to the fact that specialized media are required for its cultivation. Douglas and Gunther (1946) have designated the acne bacillus by the binomial term *Propionibacterium acnes* Its reassignment to this genus is necessary because it is an anaerobe with the morphology of a *Corynebacterium*, and ferments glucose with the production of propionic acid It is a curious fact that all the other members of the genus are found in dairy products. This organism may easily be visualized in Gram stains of smears of sebum freshly expressed from the glands of the face.

It is striking that the bacteria of the normal skin flora fall into 3 genera and include so few species One should remember however that in specialized areas such as the ear axilla and the intertriginous regions the skin flora is probably much more diversified

ANATOMICAL SITE OF THE SKIN FLORA

Bacteria are not ordinarily seen in sections of the skin stained with haematoxylin and eosin Anatomists and bacteriologists have had difficulty in demonstrating bacteria in smears or sections even after they have been deliberately placed on the skin surface (Rebell and Pillsbury unpublished) (Arnold and Bart 1934). Skin swabs which yield many bacteria on culture do not, for the most part, reveal organisms in smears This has excited interest in the actual site of the normal organisms, which are recoverable in such large numbers. These organisms evidently do not occur in or between the living cells of the epidermis. They must, therefore, be within the *stratum corneum* or in the cutaneous appendages. It may be surmised that *Propionibacterium acnes* reside in the follicular orifices and possibly in the sebaceous duct They have not been seen in the secretory portion of the gland Although Evans has clearly demonstrated by cultural survey the association of these organisms with areas rich in sebaceous glands, he offers no support for his conclusion that the organisms live within the gland itself The failure to observe organisms in routine paraffin sections when they are so abundant in sebaceous smears indicates that they are lost during the preparation of the tissue

Rebell and Pillsbury s (unpublished) quantitative cultural studies show a definite association of the aerobic micrococci with hairy sebaceous areas This implies that these organisms multiply in the upper portion of the follicle Lovell's (1945) ingenious experiments provide morphologic evidence of this He allowed freshly excised skin to incubate at 37° C for a few hours A marked proliferation of the resident flora occurred Numerous unidentified organisms were observed in the orifices of the follicles and in the sebaceous ducts. None was seen in the eccrine sweat ducts This structure is apparently not the site of bacterial multiplication unless there is blockage of the sweat duct Bacteria have never been demonstrated in the ducts except in association with miliaria Their role in this condition is probably secondary although O Brien (1950) evidently feels that they may have primary significance. A few bacteria were observed by Lovell in the *stratum corneum* of his incubated skin specimens We have been able to demonstrate the presence of cocci between the keratinized cells by means of a technique which might appropriately be called *in vivo* Gram staining This is done by applying the stains in the usual fashion directly on the skin rather than on a slide prepara

tion. The unicellular layers of keratinized cells are then removed by a successive stripping with Scotch tape.* The tape with its adherent stained scales is then directly viewed under the microscope. Micrococci may be seen in small numbers throughout the *stratum corneum*. The evidence is very strong that the main site of colonization for the resident flora is in the follicular orifice and not the *stratum corneum*. Those who have noted the great difficulty of sterilizing the skin surface by chemical and mechanical means have essentially come to the same conclusion (Lovell, 1945) that is, most of the bacteria are not on the skin surface but deep within the openings of the glandular appendages where they cannot be readily removed or killed. It is not surprising, then, that even vigorous scrubbing for one hour with rinsing every 5 minutes in acetone and alcohol during this period, did not completely sterilize the skin of 12 patients observed by Lovell. Price considers that actual sterilization of the hands would require 20 minutes of constant rubbing in a bath of 70 per cent alcohol.

THE QUANTITY OF ORGANISMS ON NORMAL SKIN

Quantitative studies of the resident flora especially of small areas, have been few. The difficulties of estimating the number of organisms accurately are great, and widely varying results have been reported. Bacterial counts of areas adjacent to each other may be extraordinarily divergent (Evans and his colleagues, 1950) (Rebell and Pillsbury unpublished). Marked quantitative variation may also be noted when the same area is sampled on different occasions. Although it is possible that these differences, which are often extreme, truly reflect a very uneven distribution of micro-organisms, it is more likely that intrinsic technical factors are responsible. While it is true that organisms such as staphylococci are typically in clusters, these aggregates are insignificantly small with regard to the size of the area sampled, usually two or more square centimetres. Evans (Evans and his colleagues, 1950) scraped the glabrous skin of the back with a scalpel, and ground up the collected material before plating it out aerobically and anaerobically. An extremely low total count of 6 bacteria per square centimetre which he obtained in one instance was in marked contrast to the highest count of another person with 865,000 bacteria per square centimetre. Differences of great magnitude were sometimes found in counts from similar areas in the same individual, as indicated by one subject whose lowest anaerobic count was 70 per square centimetre, and whose highest was 196,000 per square centimetre. The range of the aerobic count in this same individual was from 0 to 190! Despite the magnitude of these variations, there are real differences in the average number of organisms supported by the skin of different individuals. Certain persons may unquestionably be characterized as having consistently high counts while others show relatively constant low counts. Thus, the average figure for the population as a whole cannot be used for characterizing a particular individual.

Rebell and Pillsbury (unpublished) have arrived at the same conclusions using a technique of scrubbing a small area by mechanical means. The scrub machine standardizes the collection of samples as much as possible. A plastic brush is revolved within a glass cup on the skin at about 6,000 revolutions per minute

* Scotch tape: a smooth, non-fibrous, plastic tape one side of which is coated with an adhesive.—*Editor*

under a force of 30 grammes (Figs. 43 and 44). Counts from adjacent areas varied just as widely with this more precise method as with the more crude sampling techniques. Further the bacteria in a given site are not removed at a uniform

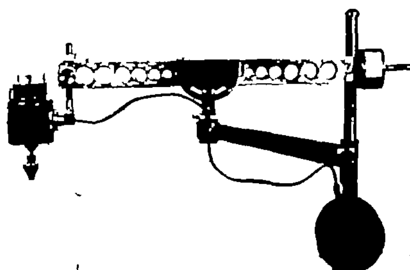


FIG. 43.—Scrubbing machine used to obtain standard samples of bacteria from the skin surface.

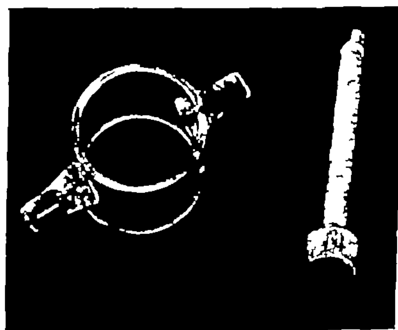


FIG. 44.—Brush and cup used with scrubbing machine.

rate. Sudden increments occur at successive intervals. This suggests either that the organisms are aggregated unevenly in pockets, perhaps in the hair follicles, or that the technical irregularities cannot be overcome. It is of interest that when

suspensions of bacteria were spread evenly upon the skin, the method demonstrated good accuracy in determinations made from adjacent areas.

Rebell and Pillsbury (unpublished) observed that 90 per cent of the bacteria removed by the Price technique were derived from the hands, the forearms accounting for the remainder. The range for 16 subjects was from 2,500,000 to 60,000,000 on the hands and forearms. Again it was possible to show that individuals had characteristic counts, some consistently low and others consistently high, in determinations repeated over many months. Not only is each individual typified by the total level of his skin bacteria, but the form of the Price curve tends to be individually peculiar. This curve, of course, reflects the rate of removal. The shape of the curve is stable even though the bacterial flora of the hands and forearms of the subjects was periodically depressed by repeated scrubbing, and the application of antiseptics. Price found, too, that over a 9-year period the flora of his arms and hands was maintained at about 8,000,000 organisms without substantial change. The total population which will develop on an individual skin is controlled by ecologic factors which are not yet understood, but it is clear that the skins of some persons regularly support more organisms than the skins of others.

Both Price (1938) and Bernstein (1948) consider that the removal of bacteria and *stratum corneum* from the cutaneous surface follows the mass action law. This law indicates that a constant fraction of the total number of cells remaining on the skin is removed with each successive scrub. The inherent error in sampling techniques and the irregularity of the cutaneous surface make it unlikely that the curves actually obtained may be accommodated into such precise mathematical formulations with any degree of accuracy. The variability in the shape of the Price curves obtained for different individuals limits the validity of the application of the mass action law to this phenomenon.

Price (1938) found a mean value of aerobic bacteria on his hands and forearms of about 3,200 organisms per square centimetre. Canuto (1937) found this to be 253 and Arnold (1942) 170. Rebell and Pillsbury estimated it at about 600. This average more nearly reflects the number of organisms on the hands. Evans (Evans and his colleagues, 1950) found a total value of aerobes and anaerobes of less than 500 per square centimetre for the backs of most individuals. Individual total counts, however, range from 10 to 800,000. Evans demonstrated that the anaerobes outnumber the aerobes studied by other investigators by 10–100 times. If, as conjectured by Rebell and Pillsbury, the total number of aerobes on the skin surface exceeds 11,000,000,000 organisms, the total skin population including the anaerobes must be enormous.

FACTORS INFLUENCING THE TYPES AND DISTRIBUTION OF SKIN BACTERIA

Sex does not influence the composition or quantity of the glabrous skin flora (Rebell and Pillsbury, unpublished). The lowest aerobic bacterial counts of the body surface occur on the non-hairy trunk. Regions with characteristically high aerobic counts are the intertriginous areas, such as the axillae, groin and gluteal cleft, and the areas with marked sebaceous development, such as the face, scalp

and upper chest Hairy areas which, of course, are often associated with areas of high sebaceous activity also favour the development of a greater population of bacteria This is also true of oily dark skins. Evans (Evans and his colleagues, 1950) concluded also that there was a positive correlation between the distribution of bacteria and the sebaceous glands. The anaerobic flora in particular reflects this. On the concha of the ear where there are many sebaceous glands and no sweat glands, the anaerobes are far more abundant than on the palm of the hand where there are numerous eccrine sweat glands, but no sebaceous glands. The aerobes, too are less common where there are no sebaceous glands or follicles as one might have surmised from the histologic evidence. One should not assume from this that sebum promotes bacterial growth Sebaceous glands empty into follicles, and it is possible that the physical qualities of these follicles account for the positive correlation between sebaceous glands and high bacterial counts. In fact there is reason to believe that sebum itself although containing substances favourable for the multiplication of lipophilic organisms, also contains substances inhibitory in various degrees to the normal skin flora

The total flora of the glabrous skin does not appreciably increase when no baths are taken for a week. There is evidence, however that lack of bathing may increase the flora in areas normally rich in bacteria, such as the intertriginous zones. It has always been assumed that the bacterial population would increase in individuals who have gone unwashed for a long period of time, but there is no real experimental support for this After the hands and arms are scrubbed by the Price technique the flora does not regain its original level for about a week (Price, 1938) It is a striking fact, however that this period may be reduced to a few hours if rubber gloves are put on at the end of the scrubbing. Presumably this accelerated restoration of the normal flora is governed by moisture. Transient increases in bacteria have been observed in individuals who were sweating in response to vigorous work under the sun (Evans and his colleagues, 1950). The slight depression of the aerobic flora noted by Rebell and Pillsbury (unpublished) during the winter months was probably influenced not only by a lower cutaneous temperature, but also by a probable reduction in the degree of hydration of the horny layer Transients such as *E coli* may become part of the resident flora of individuals experimentally kept under conditions of high humidity and temperature.

Age clearly influences the composition of the skin flora The data for very old and very young people are not adequate on this point however A small group of children studied by Evans (Evans and his colleagues, 1950) were shown to have a bacterial flora on their exposed arms which was quite different from the normal adult population. For instance, a species of *Sarcina* was predominant in some of this group although this organism was rarely encountered in adult skin. Gram-positive spore-forming rods and *Neisseria* were not uncommon in children, but were rarely found in adults In addition a non haemolytic anaerobic streptococcus was isolated which was never found in adults. Preliminary evidence indicates that the flora in bed ridden aged patients is also markedly different from that of healthy adults. Gram negative organisms in particular tend to become established.

THE INCIDENCE AND SIGNIFICANCE OF BACTERIA IN DERMATITIC SKIN

It is of importance to distinguish clinically between primary and secondary bacterial infections, though it may sometimes be difficult. The primary infections are those which originate in previously healthy skin; usually they are incited, at least in the early stage, by a single organism, and have characteristic morphologic features. The principal aetiologic role of the organism is unchallengeable in primary infections. Effective antibacterial agents produce cure promptly as a rule. Commonplace examples of such infections are impetigo, ecthyma and furuncle. On the other hand, in secondary infections, the organisms may not play a leading role in initiating the disease, but may be important in protracting and intensifying it. Usually when secondary infection complicates a pre-existing skin lesion, a mixture of organisms participates in the invasion, and the morphologic features may be variable. Unlike the more or less characteristic course of primary infections, the eventual outcome in a secondarily infected lesion will be variable, and dependent on the nature of the primary condition. Gross evidence of infection may be absent. The pre-existing skin disturbance which paves the way for secondary infection may be a type of trauma such as a cut, burn, scab or abrasion, or a previous skin disease such as contact dermatitis, seborrhoeic dermatitis, fungus and virus infections, insect bites, parasitic infestations and drug eruptions (Livingood and Mullins, 1952). The distinction between primary and secondary infection is based not only on the presence of an antecedent lesion, but on other properties as well. Thus, cutaneous diphtheria is a primary bacterial skin disease, even though it usually occurs at the site of a scratch or other disturbance of the skin. It is classified as a primary disease because cutaneous diphtheria has a distinctive course and appearance and is characterized usually by a pure culture of the causative organism, rather than a nondescript mixture. The organism may be exceedingly difficult to isolate, however, after the infection has been present for some time.

One of the troublesome issues facing the clinician is the decision as to whether or not a lesion is secondarily infected. Non-resident organisms regularly contaminate all types of skin lesions. Therefore, a new microflora is characteristic of dermatitic skin. *Certain* of the resident organisms, particularly *M. epidermidis* and *M. albus*, may persist in diseases of the skin, but the changed cutaneous environment permits certain transients to become established. The pathogenic type of *Staphylococcus* is generally predominant and is more often found as a secondary invader than any other organism (Rebell, 1947) (Cole, 1913). Haemolytic streptococci are also common colonists. Since both of these organisms are potential pathogens and are the chief transients complicating a diversity of skin diseases, the issue of their aetiologic significance is raised. It is at once clear that the mere association of these organisms with a skin lesion, even in large quantities, does not necessarily mean that significant infection exists. The problem is to separate secondary colonization from secondary infection of clinical importance. Other transients which are less often found in dermatitic skin and which may be occasionally implicated in secondary infection, include the coliforms, *E. coli* and *Aerobacter aerogenes*, species of *Proteus*, *Pseudomonas*, *Sarcina* and *Corynebacterium*. A host of other organisms may occasionally be found.

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cocci may be recovered in 6–13 per cent of the throats of normal individuals (Stuart Harris, 1948). As with the staphylococci, there is good evidence that throat carriers contaminate their skin. The infrequency of *beta*-haemolytic streptococci on normal skin as compared to staphylococci is possibly due both to the lower incidence of upper respiratory carriage and to the superior capacity of the normal skin to destroy this organism. Rebell's (1947) study of various lesions of the feet and hands indicates that *beta*-haemolytic streptococci colonize dermatitic skin less frequently than do coagulase-positive staphylococci. The human pathogen type belonging to Group A tends to be associated with suppurative, intensely inflamed lesions.

SECONDARY INFECTION

What criteria should be used for determining whether staphylococci and streptococci are causing secondary infection?

It must be clear from the foregoing data that cultures alone are not too helpful. In fact, pathogenic streptococci and staphylococci may be anticipated in cultures taken from exudative eczematous skin. We have been repeatedly surprised at the large number of organisms which may be recovered from lesions which clinically do not seem infected. Indeed, many lesions swarming with pathogenic bacteria may heal with remarkable rapidity even though no antibacterial measures are taken. The mere recovery of the organism then, has no positive significance in determining its aetiologic role. It is necessary at this point to restate one of the basic features of the host-parasite relationship in attempting to define the pathogenicity of a disease-inciting organism. *The manifestations of disease are due to the reaction of the host to the disease-inciting agent* The actual expression of the disease is consequent upon the changes induced in the host by the bacteria. If the host does not react, there is no disease. The presence of large numbers of certain bacteria in dermatitic skin is significant only when it can be shown that some damage has been produced, or that the host defences have been brought into play In ascertaining whether secondary infection has actually occurred, then, a method has to be found which enables one to detect by laboratory or clinical means the defensive reactions of the host.

We have been impressed with the considerable usefulness of a very simple method. This is the smear technique. A moist swab is rubbed vigorously over the surface of the lesion and a Gram stain is made of the smear Our preliminary experience with this method may be summarized as follows. In lesions which are clearly secondarily infected, that is, when there is gross suppuration, large numbers of bacteria and polymorphonuclear leucocytes are found. Bacterial phagocytosis by the leucocytes is good evidence of the defence reaction in operation. Although leucocytes do not necessarily indicate a specific reaction to bacteria, their simultaneous occurrence with bacteria increases the likelihood that they were called forth in response to infection. When numerous colonies may be cultured from a lesion, the organisms are readily visualized in direct smears. In fact, although specific identification is impossible, the recognition of staphylococci streptococci and Gram-positive and Gram-negative rods is a simple matter There is good agreement between the smear and culture method in determining the kinds and numbers of bacteria present. Certain lesions, such as acne pustules may exhibit large numbers of polymorphonuclear leucocytes

Since the pathogenic staphylococcus (coagulase-positive *Staphylococcus aureus*) and the *beta*-haemolytic streptococci are most often significant clinically the following discussion is largely confined to these organisms One should be mindful however of the opinion of Livingood and Mullins (1952) that infections due to *Proteus* and *Pseudomonas* are probably increasing

Although the coagulase-positive *Staphylococcus* is not a true resident organism, it is well known that it may be recovered on normal skin Reference has already been made to Williams (1946) findings in which this organism was recovered from 70 per cent of normal individuals when 11 different skin sites were sampled Gillespie, Devenish and Cowan (1939) Martin (1942) and Rebell (1947) record a normal incidence of 20–25 per cent, although attention should be drawn to the fact that most of these carriers had rather small numbers of organisms. The most common reservoir for these organisms is in the upper respiratory tract. Miles, Williams and Clayton-Cooper (1944) found pathogenic staphylococci in the nose of about 45 per cent of 1 000 normal adults. Others give somewhat lower figures (Gillespie, Devenish and Cowan, 1939) Further as Miles, Williams and Clayton-Cooper (1944) and Moss, Squire and Topley (1948) have shown, there is a positive correlation between nasal and skin carriage The organisms in the nose and on the skin have been shown to be of the same type by bacteriophage typing. Moss Squire and Topley reduced the skin carriage rate by eliminating the organisms in the nose with a 10-day course of intranasal penicillin (Moss, Squire and Topley 1948) All these facts indicate that nasal "carriers" continuously contaminate the exposed cutaneous surface, particularly the wrists.

On diseased skin, by contrast, *Staphylococcus aureus* may grow luxuriantly It is recovered from the great majority of dermatitic skins. Storek (1948) found coagulase-positive *Staphylococcus aureus* in 92 per cent of eczematous lesions. Rebell (1947) reported an incidence of 35–93 per cent in various lesions of the hands and feet which were not primarily bacterial in origin Seventy five per cent of the vesicular eruptions of the hand yielded *Staphylococcus aureus* Others have noted this, including Fowle and Rice (in press) who are impressed with the great abundance of this organism in lesions of nummular eczema. Exudative and inflammatory lesions, in particular promote its growth Chronicity is also a promoting factor It is less often found in abundance in lichenified dry lesions. Its presence, then is related to the degree of disturbance of the integrity of skin and the persistence of the basic disease. We are, of course, excluding from consideration primary bacterial diseases which are initiated by this organism

Beta-haemolytic streptococci are not common on the normal skin. These streptococci may be divided into a number of groups, presently ranging from A to N on the basis of a group specific carbohydrate antigen. The organisms in Lancefield's group A are the principal human pathogens. Groups B C and G which are also haemolytic, are primarily pathogenic to animals, and cause human disease infrequently Hare (1941) recovered haemolytic streptococci from the skin of 6 per cent of normal individuals, but only one of these belonged to the human Group A type. Strains B C and G were more common on the normal skin Colebrook Maxted and Johns (1935) did not find any Group A haemolytic streptococci on the normal skin unless the individuals were suffering from colds The low incidence of *beta*-haemolytic streptococci particularly of the human pathogenic type, on normal skin was also noted by Rebell (1947) Group A strepto-

lation are, in our opinion, essentially unknown. Heretofore, the chief interest has been centred on determining the inhibitory forces. In the largest sense, we are not so much concerned with why certain organisms do not proliferate on normal skin, as with how those that do multiply on the cutaneous surface are able to do so. What factors in the soil stimulate their reproduction and growth?

Two principal theories have been championed by investigators of this question; One school ascribes the self-disinfection power of the skin to chemical agents, such as fatty acids contained in the sweat or sebum; the other school holds that the responsible factors are chiefly physical. One of the chemical theories which has attracted wide notice is Marchionini's (1928, 1929) "acid mantle" hypothesis. Marchionini and his co-workers thought that acids present in sweat and the low iso-electric point of keratin governed the acidity characteristic of normal skin. They postulated that these acids formed a mantle which acts as a barrier against bacterial invaders. Perhaps part of the great popularity of this theory is due to the engaging and felicitous slogan, "the acid mantle". Many protective properties which have little or no support in experimental fact have been ascribed to this mantle. There are data which cast doubt on the correctness of this theory. Cornbleet (1934), for instance, showed that staphylococci and yeasts could multiply in sweat adjusted to *p*H 3. As for Marchionini's observation that applied bacteria disappear more slowly from the normally more alkaline intertriginous area, this phenomenon may be not so much due to the greater disinfecting power of acid skin as it is to the enhancing effect on bacteria of the greater moisture of the intertriginous regions. In an earlier study Cornbleet (Cornbleet and Montgomery, 1931) demonstrated that opposing surfaces which constantly remain moist, such as the region under the female breast, have an impaired self-disinfecting mechanism; such surfaces regain this power when exposed to the air. The antimicrobial properties of the acid mantle have also come under critical examination by Pillsbury and Rebell (1952). These workers found that coagulase-positive staphylococci and gram-negative rods have the same *p*H tolerance as normal skin micrococci, whereas one might have expected the resident organisms to be more resistant to a lower *p*H. These organisms grew equally well in the *p*H range of 5–6 characteristic of the normal skin surface. Residents and transients alike were inhibited at *p*H 4·0. A disconcerting finding was the failure of normal skin diphtheroids to grow at *p*H 5. *In vivo* these organisms colonize at this level of acidity. Thus, this species tolerates a condition *in vivo* which is not tolerated *in vitro*. This experience illustrates the great difficulty of evaluating *in vitro* results, particularly when a single factor such as *p*H is regarded as the controlling one. If acidity controls the types of organisms which can multiply on the skin's surface, it is difficult to understand how the resident corynebacterium are maintained under such unfavourable circumstances.

Arnold (1930) found the skin of cadavers to have less disinfecting power than that of living persons. He consequently believes that living skin has a unique degerming capacity. Burtenshaw's (1945) work added weight to the chemical theory of disinfection. He prepared ether extracts from skin, hair and nails, and found them to be strongly bactericidal for *beta*-haemolytic streptococci, but harmless to *E. coli*. Some strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* were partly inhibited, while others were not. Burtenshaw concluded, after demonstrating that the active component of the lipoid extract lay in the fatty

without bacteria. On the other hand, and this is the crux of the matter the smears of many lesions which clinically do not suggest the presence of secondary infection often show large quantities of organisms, particularly staphylococci, with no or little leucocytic response. Phagocytosis is minimal or absent. We consider that significant secondary infection probably exists when both bacteria and phagocytosing polymorphonuclear leucocytes are present in abundance in the smear The presence of either one alone has no particular clinical significance The effect of this simple test is to make the criteria for judging the presence of secondary infection more severe In our opinion the smear technique is often simpler and more informative than cultures

Some rather interesting questions are brought up by the innocent contamination of dermatitic skin with pathogenic organisms which though present in abundance, may not seriously influence the course of the primary lesion Coagulase-positive staphylococci elaborate a cell killing exotoxin as well as other poisons, which destroy leucocytes and red blood cells. It seems strange that large numbers of staphylococci multiplying in dermatitic skin should ever fail to cause damage. Either the toxins are not always produced in large enough amounts or the body may contain sufficient antibodies to neutralize them. As always, in any infection, the outcome depends upon the balance attained between the forces of the host and the parasite. Antibodies and antitoxins are almost always present to some degree in the sera of individuals beyond one year of age. With internal staphylococcal infections a sudden rise in agglutinin or antitoxic antibodies signifies recent infection Such an immunologic test might be expected to be a useful means of distinguishing between contamination and true secondary infection of the skin. Unfortunately infection of the skin with staphylococci is ordinarily not a sufficient stimulus to antibody production, and the immunologic tests are not useful clinically (Dolman, 1933)

In a similar manner the capacity of haemolytic streptococci to produce disease is related to the elaboration of haemolysins, fibrinolysins leucocidins, and other principles Antibodies to the fibrinolysin and haemolysin antigens are increased following an acute infection in an area such as the throat (Todd 1932) In fact the demonstration of such responses has been of the greatest value in distinguishing simple carriage from actual infection Spink and Keefer (1936) have demonstrated that anti fibrinolysins and anti haemolysins increase during the course of erysipelas There is no evidence however that this occurs to a degree to be diagnostically useful with the more superficial streptococcal infections of the skin

THE DE-GERMING CAPACITY OF NORMAL SKIN

Bacteria placed on normal skin die rapidly They lose their viability and fail to multiply This has led to the concept that the skin has intrinsic mechanisms for self-sterilization The *modus operandi* of this self-disinfecting or degerming power has been a subject of much investigation. Burtenshaw (1948) has reviewed the problem in detail It has been more or less assumed that this degerming capacity is one of the important ecologic factors which enable the normal resident flora to be maintained The situation however is more complicated than this. The dynamic factors which govern the composition of the normal skin flora and the means by which potential competing organisms are kept out of the resident popu

These workers were concerned with degerming the skin by surgical scrubbing. They pointed out that the term "degerming" as originally used by Price, refers to the removal of bacteria either by mechanical means, as by scrubbing with soap and water or by actual killing with germicides. It had been found that low counts were obtained by the Price technique after the application of quaternary ammonium compounds. This was interpreted to mean that the bacteria on the skin had been destroyed. This was not the case, however. If, instead of scrubbing with water alone in the basins, following the application of a quaternary compound, soap was used, there was an immediate and considerable increase in the count. To explain this, Miller and his colleagues (1943) assumed that the bacteria were not killed by the quaternary ammonium compound, but were actually protected under a residual film. This film remained intact unless it was exposed to soap or alkalis. The actual physical existence of this film was not demonstrated. Blank and Coolidge have given a more plausible explanation of this phenomenon. They showed that the quaternary ammonium compounds change the electric charge of the cutaneous surface to positive. Because the bacteria are normally negatively charged, such a change will result in attraction between the bacteria and the keratinized cells, and interfere with the release of the bacteria from the cutaneous surface. According to this theory the cutaneous surface will be negatively charged at any *p*H higher than the iso-electric point of keratin which is normally in the *p*H range of 3.7–4.5. Since the skin surface is generally at a *p*H higher than this, it will normally have a negative charge and consequently there will be a certain degree of repulsion between bacteria and keratin. A suspension of keratinized cells moves toward the anode under the influence of an electric current, proof that the negative charge exists. This movement is reversed in the presence of quaternary ammonium compounds. The keratinized cells now migrate to the cathode. In an ingenious experiment Blank and Coolidge showed that wool would attract bacteria out of a suspension if it was pre-treated by quaternary ammonium compounds. This endows the wool with a positive charge, causing bacteria to be attracted. The attracted bacteria could be released by exposure to strong alkalis. These restored the normal negative change of keratinized surfaces. The magnitude of the negative charge is directly proportional to the *p*H. Therefore strong alkalis, such as soap and trisodium phosphate, by inducing a negative charge, facilitate the mechanical removal of bacteria from the skin surface. Thus, the value of soap in removing bacteria has been explained in an altogether unsuspected manner.

These experiments also may explain the earlier work of Arnold (1942) in an interesting way. Arnold found that if he dipped his thumb in 1 per cent sodium carbonate and then placed the thumb on a culture plate, several hundred colonies developed. If the thumb was immersed in 1 per cent hydrochloric acid, almost no colonies developed at the site of contact with the culture medium. In an experiment very similar to that carried out by Blank and Coolidge with wool cloth, Arnold found that after exposure to acid, his hands would attract bacteria. When he placed them in a suspension of *Bacillus prodigiosus* after such treatment, the bacterial count in the suspension was reduced. On the other hand if the surface of the hand was alkalinized, the organisms were not attracted to the skin, and the counts in the suspension did not fall. To explain these findings, Arnold postulated that the stratum corneum behaves as a colloidal gel. Alkalinity brings about

acid fraction that it is these substances which endow the skin with its disinfecting power Obviously this could not account for everything, as Burtenshaw implies, since some normal skin organisms were inhibited on the one hand, and certain transients such as *E coli* were resistant

Norton and Novy (1931 1932) were the first to marshal evidence that the so-called self-disinfecting mechanism of the skin was due to desiccation. They showed that the decrease in viable organisms coincided with the drying of the suspension occurring within the first ten minutes. In other words, drying and loss of viability were simultaneous. When the skin could be judged dry then the "sterilization was about complete. On glass surfaces the bacteria were killed almost as rapidly as on living skin Little reduction occurred when the skin was deliberately kept moist. Rebell and his colleagues (1950) have forcefully supported Norton and Novy s ideas in their recent studies. They performed a number of experiments which convinced them that the self-disinfection mechanism was non-specific and entirely attributable to desiccation in so far as *E. coli* and staphylococci were concerned They showed by quantitative studies that certain bacteria placed on the skin were considerably protected when the area was kept moist with an atomizer Furthermore, there was no reduction of coagulase-positive staphylococci when the organisms were suspended in serum before being applied to the skin In fact there was occasional multiplication The serum film delayed desiccation A similar but less significant effect was produced by glycerin which because of its water holding capacity reduced the rate of desiccation Although *E coli* was shown to be much more sensitive to the effect of desiccation than coagulase positive staphylococci these species were killed by desiccation on glass at about the same rate as on skin The protective effect of moisture on bacteria of the skin was strikingly demonstrated by placing human subjects in an insulated room for 8 hours at a temperature of 96 F and a humidity of 99 per cent *E coli* applied to the skins of these subjects did not disappear In fact, it could be recovered from the skins of a majority three weeks later Thus, it was actually possible for *E coli* to become established in the microbial community after being applied in an environment of heat and humidity Rebell and his colleagues found that normal skin micrococci were reduced at the same rate as coagulase positive strains of staphylococci This implies that under the conditions of the experiment the skin does not differentiate between a resident and a transient organism One should point out however that almost all these studies involved a very short period of time, usually not exceeding 15 minutes after the application of bacteria Also the skin of the subjects may be considered to be supporting a maximum population of organisms before the suspensions are added Obviously the problem is not a simple one, and later studies suggest that Rebell and his co-workers may have placed too much emphasis on desiccation as a universal mechanism applicable equally to all bacteria Arnold and Bart (1934) previously had found no difference in the rate of disappearance of bacteria when the skin was kept moist in a humid incubator than when evaporation was allowed. They do not consider desiccation to be very important Arnold and Bart s repudiation of the importance of moisture lacks confirmation and would not appear to be in good agreement with data from other sources

The recent work of Blank and Coolidge (1950) reveals still another factor which has a marked effect on the rate at which bacteria disappear from the skin surface.

for a day or more, but were even able to multiply on the moist skin. For these organisms, desiccation was a highly significant factor.

From the experiments of Ricketts and his colleagues, it is seen that moisture apparently does not influence the rate of disappearance of *Staphylococcus aureus* greatly. Under both nylon and polyethylene plastic covering, this organism generally persisted for a day but was slowly reduced to the point of extinction on the third day. With careful measurements, however, it was shown that more staphylococci remained on the skin at the end of 24 hours under humid conditions. This may indicate that desiccation is an accessory factor in the killing of staphylococci. The real significance of this work lies in the recognition of the varying behaviour of different organisms in response to changes in the moisture of the skin surface, something which previous workers had not taken sufficiently into account.

Ricketts and his colleagues then studied the effect of saturated and unsaturated fatty acids obtained by fractionating sebum. They found *Streptococcus pyogenes* remarkably sensitive to the unsaturated acids whereas, *Staphylococcus aureus* was very much less sensitive, and *E. coli* and *Pseudomonas* fairly resistant. Higher concentrations of saturated fatty acids were required to kill these organisms, although the spectrum of sensitivity was about the same. They then showed that oleic acid was present in significant quantities in human sebum and finally demonstrated that this acid gave results which were quite similar to the effects of the unsaturated acid fraction of sebum. Oleic acid, thus, was implicated as an agent which probably destroys streptococci. It will be recalled that Burtenshaw (1945), too, recognized the extreme sensitivity of streptococci to fatty acid fractions prepared from sebum, as well as the increased resistance of *Staphylococcus aureus* and, even more markedly of *E. coli*. Pillsbury and Rebell (1952) showed that the normal skin bacteria, as well as coagulase-positive staphylococci and Gram-negative rods, were inhibited by strong concentrations of caprylic and undecylenic acids. In this work, also, the comparative resistance of the Gram-negative rods to fatty acids was demonstrated. The cutaneous fatty acids are probably not important in freeing the skin of *E. coli*. Ricketts and his co-workers found that the normal skin residents were less sensitive to oleic acid and to the unsaturated fatty acid fraction of sebum than *Staphylococcus aureus*. Thus, it would appear that these chemicals on the skin's surface are less *hostile* to the normal residents than to certain pathogenic transients.

Serum albumin was shown to neutralize the antibacterial effect of oleic acid. When streptococci were suspended in serum albumin before being applied to the skin, there was a considerable degree of protection. Thus, the *in vitro* and *in vivo* results are similar. The obvious clinical implication of these findings is that streptococci may persist much better in dermatitic skin because the fatty acids to which they are sensitive are inactivated by serum. While Rebell and his colleagues (1950) concluded that the protective effect of serum was due to the prevention of rapid desiccation, the additional factor of inactivation of bacteriostatic fatty acids is also significant, especially for some organisms. Since *Staphylococcus aureus* is only moderately sensitive to fatty acids and more resistant to the effect of desiccation than Gram-negative rods, its opportunities for becoming established on normal and dermatitic skin are enhanced. *Streptococcus pyogenes* survives better on normal skin for a few hours when the skin lipids are removed by prior treatment with acetone. The sebaceous film is replaced within an hour or two after its

water absorption swelling, and resultant release of bacteria Acidity contrariwise, causes a contraction of the *stratum corneum* and prevents bacteria from leaving the surface. Although this theory may have some merit, it would seem that the effects noted by Arnold may be more satisfactorily explained on the basis of the findings of Blank and Coolidge. Using this hypothesis, it is evident that bacteria would not be released from the cutaneous surface after treatment with a strongly acid solution because the pH is probably reduced below the iso-electric point of keratin A positive charge would result and there would be an attraction between the keratin and the negatively charged bacteria On the other hand, exposure to alkaline solutions increases the negative charge of the *stratum corneum*, and repels the bacteria. Regardless of which of these explanations is correct, the studies of Arnold and of Blank and Coolidge illustrate very well the complexities which may be encountered in studies of the removal of bacteria from the surface of the skin It would appear for instance, as Arnold showed, that the resident flora seems to disappear after treatment of the skin with 5 per cent acetic acid These organisms had not been killed but were simply being held on the skin surface, as was easily shown by treating the same skin with strong alkalis, and releasing the bacteria in abundance. It is obvious that physical factors, as well as chemical ones must be considered in studies dealing with the removal of bacteria from the cutaneous surface. Some support of Arnold's hypothesis of the importance of the degree of swelling of the *stratum corneum* is afforded by the experiments of Cromwell and Leffler (1942) With the Price technique, using 10 per cent alum, they found that the removal curves were similar to those obtained with 70 per cent alcohol They did not fall into the trap of misinterpreting this to mean that alum was as good a degerming agent as alcohol. It merely hardened the *stratum corneum* and this prevented removal of the bacteria. Mercurial compounds undoubtedly act in a similar way as was shown by Price, and their clinical usefulness as antibacterial agents on the skin is extremely doubtful.

Ricketts and his group (1951) have performed an important service in reconciling some of the previously divergent findings and points of view by showing that both desiccation and chemical sterilization may be variously important *depending on the organism studied* The experimental approach used by them was more adequate, in several ways First, a period of days instead of minutes was used to determine the fate of bacteria placed on the skin Secondly they protected the site of application under two different types of transparent coverings. One covering was nylon, which is permeable to water and under which the skin remained dry The other covering was a polyethylene plastic which prevented evaporation and allowed the skin to remain moist. By this ingenious method they were able to study the effect of skin moisture on the survival of bacteria more accurately than had been done before. The bacteria used were *Streptococcus pyogenes* *E. coli* *Pseudomonas pyocyaneus* and *Staphylococcus aureus* Under the nylon covering (dry skin), staphylococci were the only organisms which persisted for more than one day but they did not survive for more than three days. On the other hand under the polyethylene plastic covering (moist skin) *Streptococcus pyogenes* was the only organism which was not recovered after one day This organism therefore, dies out in less than a day whether the skin is wet or dry and clearly some factor other than desiccation must be responsible. *E coli* and *Pseudomonas* not only persisted

illustration is the contention that various eczematous and pustular eruptions frequently arise from sensitization to bacteria in focal infections. In connection with this question it may be worthwhile to review briefly the sensitization syndromes which bacteria or their products may bring about.

Both anaphylaxis and the Arthus phenomenon may be induced in animals by many different types of killed organisms or their products (Freidberger and Mita, 1911 Baker Thomas and Pemek, 1935). Such reactions, however are not necessarily representative of those which occur during the natural course of infection, and the sensitization produced is no different from that obtainable with proteins from any other source.

Tuberculin allergy

The sensitivity of the skin which is associated with tuberculosis furnishes a prototype of infection allergy. This refers to the sensitization induced by actual infection. The intracutaneous injection of tuberculin elicits a delayed inflammatory response in the tuberculous host. Tuberculin sensitivity may be transferred by injecting cells from the tuberculous animal into a normal recipient. Passive transfer by means of serum is not possible, as it is with hypersensitivity characterized by the immediate wheal response (Seegal, 1949) The cells of tuberculous animals are inhibited by tuberculin in tissue culture (Rich and Lewis, 1932). Lymphocytes from tuberculous animals are lysed by tuberculin. Finally the injection of tuberculin into tuberculous persons or animals may incite focal inflammatory reactions in the areas of active infection.

Clinically tuberculin allergy may result in different kinds of spontaneous "ids" These "ids" are sterile, distinctive lesions which are truly secondary to a primary focus of infection. The Koch phenomenon is another biologic feature of tuberculin allergy which is noteworthy for its clinical implications. The significance of this phenomenon lies in the increased capacity of the re-infected animal to dispose of bacteria. Thus, while the primary cutaneous lesion of tuberculosis takes a long time to heal, and involves the regional lymph nodes, the re-inoculation lesion is more inflammatory the organisms are more rapidly killed, and healing occurs without involvement of the lymph nodes. The classical interpretation attributes this altered course of events to allergy although Rich (1944) has presented weighty arguments against this thesis. In any case, this altered reactivity evidenced when the host is exposed for a second time to the same organism, is an intrinsic characteristic of bacterial allergy

Other chronic infections have been shown to possess certain of the characteristics of tuberculin allergy and are considered to be representative of this type. Leprosy for instance, had many clinical features which are similar to tuberculosis. Chronic fungus infections, such as coccidioidomycosis and histoplasmosis are characterized by the tuberculin-type allergy Erythema nodosum is a clear-cut example of an allergic skin lesion which is commonly seen in primary coccidioidomycosis and other invasive infections. The reproduction of this lesion by the injection of coccidioidin into hypersensitive individuals with the active disease clearly establishes its allergic origin. Erythema nodosum is, in primary coccidioidomycosis at least, an id reaction secondary to a primary focus of infection. This is not to say that diseases characterized by the tuberculin type of allergy are similar in all respects.

removal, but during this time, streptococci are not killed as rapidly On the other hand, the marked decrease in the disappearance rate of *E. coli* found by Rebell and his colleagues following the prior removal of skin lipids with ether cannot be attributed to the removal of antibacterial fatty acids, since this organism is resistant to these substances. It is possible, as they suggest that this was due to a lowering of the skin temperature or perhaps to the enhanced opportunity for the organisms to penetrate into the follicular openings following removal of surface lipids

Ambiguities are bound to arise when single factors studied *in vitro* are applied to complex *in vivo* systems Pillsbury and Rebell's (1952) finding that sebum had a mild inhibitory effect on normal skin micrococci *in vitro* is disconcerting in view of the well-established fact that these organisms reside in close association with the sebaceous duct. Burtenshaw also found a normal skin organism, *Micrococcus epidermidis* to be inhibited inconstantly by a fatty acid fraction of sebum Perhaps just as serum inhibits the antibacterial effect of fatty acids, so on the normal skin surface there are substances, probably proteins, which do the same thing.

The following conclusions may be drawn from the sometimes complex and divergent studies of the mechanism of the degerming phenomenon, as summarized above. The rapid disappearance of *Streptococcus pyogenes* is probably due at least in part to the chemical sterilizing effect of fatty acids contained in sebum, particularly the unsaturated fraction Desiccation and not chemical sterilization, would appear to be a significant factor in producing disappearance of Gram-negative organisms. Both desiccation and chemical effects influence the rate of disappearance of *Staphylococcus aureus* The presence of an exudate or serum interferes with the normal mechanism by which streptococci and staphylococci are inhibited. The exudate would operate both by inactivation of the fatty acids in respect to antibacterial effect, and by preventing desiccation. There can be no question as to the important effect of moisture in nourishing some bacterial strains, and it is readily understandable why intertriginous areas support a larger number of bacteria than do dry surfaces and why the inherent degerming effect of the skin in these areas is impaired It must be emphasized in all this that there are many gaps in our knowledge of this subject A few facts having direct clinical application are known, and some of the data permit the formulation of useful hypotheses in understanding how the skin defends itself against bacteria Little is known about the factors which permit a few species of bacteria to grow on normal or dermatitic skin to the exclusion of other species. A great deal more remains to be learned about the forces which control the bacterial ecology of the surface of the skin.

BACTERIAL ALLERGY IN THE PATHOGENESIS OF SKIN DISEASES

The role of sensitivity of the skin to bacteria in the pathogenesis of various cutaneous lesions is an exceedingly controversial subject. A small amount of fact and a large amount of theory have produced discussions which have yielded more heat than light While it is well known that there are demonstrable lesions due to sensitivity to bacteria occurring in the course of chronic infections such as tuberculosis, the speculations that lesions such as boils may be primarily a hypersensitivity reaction to bacteria have unstable experimental foundations. Another

As has already been pointed out, an increasing inflammatory response is characteristic when the hypersensitive animal which is exposed to an organism for the second time. This reactivity is increased with repeated infections. It is of interest that Boe was unable to produce furunculosis in rabbits by applying living bacteria to the skin of highly sensitized animals.

It is important to differentiate in this respect between sensitivity reactions elicited at the site of multiplication of the organism and those occurring at a distance from the primary site. Other instances in which the allergic reaction supposedly occurs where the organisms are growing are re-inoculation tuberculosis and re-inoculation ringworm in animals. While this may be true of tuberculosis and certain other infections, staphylococcal and streptococcal infections have little in common with tuberculosis and do not seem to exhibit the features of infection allergy as outlined for tuberculosis. The fact that an inflammatory reaction occurs at the site of injection of killed staphylococci reflects hypersensitivity of the individual. It does not necessarily mean that the same reaction takes place in natural lesions. It has been found, for instance, that even though animals are desensitized to vaccinia virus, reinfection with this virus still produces a hyper-inflammatory rapidly developing lesion, even though the tissues are presumably no longer allergic (1952). Dermatologists and allergists often attempt to desensitize individuals suffering from recurrent staphylococcal infections by a series of injections of staphylococcus toxoid and vaccine. This is a well-established practice for sycosis barbae and recurrent furunculosis. The real value of such treatment is, however questionable. In the first place, desensitization is difficult to achieve, although with perseverance in treatment the skin does acquire more tolerance to the organism or its toxin. Boe (1945) himself recorded experiences which would seem to contradict his major thesis. He was able to desensitize three patients with strong hypersensitivity to *Staphylococcus aureus* by the intravenous injection of a straphylococcal filtrate. Sycosis barbae in one patient remained unaltered, and in another with recurrent furunculosis there was only temporary improvement which could have been spontaneous. Altogether both clinical and laboratory experience do not support the view that hypersensitivity significantly influences primary staphylococcal infections Hypersensitivity to staphylococci and streptococci could induce disease in still another fashion that is, either by the production of "id" reactions secondary to a primary focus of infection, or by inducing allergic reactions in eczematous lesions which these organisms have colonized Andrews (1934) has strongly championed the "focus of infection" theory He believes with Barber who first described pustular bacterid, that these lesions are secondary to a focus of infection, usually in the teeth or tonsils. Others, however have not had any consistent therapeutic successes following the removal of the presumed focus of infection. The fact that these patients are cutaneously reactive to staphylococcus and streptococcus cannot be considered as necessarily significant in view of the large percentage of normal individuals who give such reactions.

Chronic urticaria is another refractory disease which is often attributed to foci of infection This cause can rarely be proved. Andrews also considers that foci of infection are very important aetiologically in pustular acne. The theory of focus of infection has possibly been over-emphasized by some. It is often invoked when no other aetiologic agent can be found, as in persistent eczematous eruptions. Mitchell-Heggs (1950) has answered the objections of those who stubbornly insist

The basic clinical characteristics of the tuberculin type allergy are its natural induction, the existence of ids and focal reactions, and the altered course of events upon re-infection These qualities will furnish the basis of comparison for considering the nature of other reactions which are attributed to bacterial allergy

Bacterial allergy to organisms commonly causing skin infections

Staphylococci and streptococci will be the principal subjects of this discussion since they are the commonest causes of primary and secondary skin infections. Sensitivity to these organisms is easily demonstrated by intracutaneous tests. Kobak and Pilot (1931) found that 99 per cent of mothers reacted to *Staphylococcus aureus* filtrates and vaccines. Newborn babies did not react but after two months the incidence of reactivity increased. The gradual increase of positive reactors to streptococci in relation to age has been shown by MacKenzie and Hanger (1974). Data from many sources indicate that a considerable number of adults are hyper sensitive to staphylococci and streptococci These reactions are of both the delayed and immediate type (Swineford and Holman, 1949). The commonness of the immediate reaction to bacterial antigens has not been sufficiently appreciated. The immediate reaction may be passively transferred by serum. In a series of 3 860 intracutaneous tests with polysaccharides and nucleoprotein fractions of 14 species of bacteria, Holman and Swineford (1949) demonstrated a large number of immediate and delayed reactions These reactions were just as striking in individuals without obvious infection or allergy as in patients with typical allergic syndromes Others have found immediate reactions more common in allergic individuals than in normal persons (Kraft, Mothersill and Nestman, 1949). Most normal individuals gradually become reactive to a host of bacteria normally found in the external and internal environment. The high incidence of bacterial sensitization is presumed to be due to repeated immunologic experiences such as sore throats skin infections and life long exposure to bacteria residing in and on the body It has not been established that the incidence of cutaneous reactivity to staphylococci and streptococci is greater in individuals with diseased skin than in normal individuals. In fact individuals with staphylococcal infections are occasionally non-reactive.

Boe (1945) maintains that the typical lesions of staphylococcal infections represent allergic reactions of the host The uniqueness of this idea is that the pathologic tissue response is not attributed to the virulence of the organism and to the liberation of toxins and substances upon which virulence depends. The hyper sensitivity reaction instead is the crucial feature which makes the lesion possible. Coggi (quoted by Boe) is another investigator who stresses that hypersensitivity is the principal cause of the typical manifestations of staphylococcal infections. Boe supports his theory by showing that individuals with staphylococcal infections have a considerable hypersensitivity to intact dead organisms. This thesis has many weaknesses. No one has succeeded in producing a furuncle by injecting dead bacteria, although this should be possible if the lesion is entirely allergic. Furthermore, one might expect to show that as sensitization was increased by repeated infection as in recurrent furunculosis the disease would become correspondingly more severe. Further it is not apparent that the tissues react in a different way to reinfection than to the primary infection The evolution and course of primary furunculosis is probably not distinguishable from recurrences.

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our policy therefore, to expose such areas to the air as much as possible and, particularly to avoid the application of occlusive dressings which may become soggy from serum, perspiration, or water

(5) A further source of moisture is through sweating. There is the added complication of sweat-duct obstruction which invariably occurs as the result of any moderate injury to the skin, or from any dermatitis. The best, indeed the only method of preventing this is to reduce sweating by keeping the patient in as cool an environment as possible. This is of particular importance, in our opinion, in the treatment of infants, who are often maintained, to their detriment, in an artificial tropical environment.

(6) It is of the greatest importance to recognize acute secondary infection of a dermatitis as quickly as possible, and to treat it adequately If the infection is allowed to run unchecked for several days or weeks, the responsible organism may become firmly established as part of the resident flora.

(7) If an area of chronic dermatitis or other eruption has become chronically infected with pathogenic bacteria, it is practically impossible to dislodge these bacteria unless the integrity of the skin is returned to normal. Even then, the pathogenic bacteria may be recoverable from the area for very long periods.

(8) If it is considered advisable on clinical grounds to undertake antibacterial therapy in the treatment of dermatitis or eczema, careful bacteriologic study is often well worth while. Study by the smear technique as outlined on page 199 is suggested. If cultures are taken, every effort should be made to determine which bacteria are chiefly responsible for the infection noted, and the respective sensitivity of these bacteria to various antibiotics determined It is not considered advisable simply to use a succession of antibacterial agents externally or internally this represents a type of shotgun therapy which may have definite recoil effects in terms of sensitization of the patient, and of increasing the resistance of bacterial strains to certain antibiotics.

(9) The methods of determining the clinical significance of sensitivity to bacteria recovered from dermatitic skin are unsatisfactory Nor is it clear that attempts at producing hyposensitization by the injection of vaccines or denatured toxins have any regular good effects. Indeed, the effects at times may be harmful.

(10) The general tendency to regard chronic otitis externa as a fungus infection is unfortunate. True fungus infections of the external ear are rare. The application of antifungal preparations will, therefore, not be effective. If they are irritating, such treatment will do harm. It is of importance to determine whether or not the external otitis is related to middle ear disease, or is a localized expression of dermatoses such as seborrhoeic dermatitis, eczematous contact dermatitis, psoriasis, neurodermatitis, or apocrine gland retention syndromes.

(11) In the treatment of any cutaneous infection, it would appear that the following general rules may apply on the basis of present evidence.

(a) It is of the greatest importance to avail oneself of every measure to make the skin as inhospitable as can be to the pathogenic bacteria. These factors have been mentioned above, and include dryness, avoidance of mechanical or chemical irritation in so far as possible, proper treatment of the underlying dermatosis, and avoidance of topical sensitizing medication.

(b) Cleansing and degerming of the skin by simple measures is fully as important as any specific antibacterial medication if not more so. Soap and water and

on proof of a focus of infection when this cause is invoked by citing the existence of antigen-producing resident bacteria in the nose and throat Thus for him, cutaneous lesions may be caused by a sensitivity to bacteria in the absence of a localized focus of infection since the resident organisms can supply enough antigen to produce disease. While certain eruptions may occasionally disappear following the removal of a focus of infection the cause-and-effect relation of this phenomenon is not always clear It is our opinion that the theory of foci of infection in relation to cutaneous diseases requires more substantial evidence before it can be accepted without several compelling reservations

SUMMARY AND CLINICAL IMPLICATIONS

The foregoing material has many direct clinical applications. By way of summary therefore, the following statements seem appropriate We shall include certain principles in regard to the management of pyogenic infections derived from our own experience and that of others, particularly Livingood.

(1) It is abundantly clear that in order to maintain a benign "normal" bacterial flora, the skin must remain healthy and intact. Temporary disturbance of its integrity by injury unless extremely severe, is ordinarily easy to deal with because the skin has remarkable restorative and recuperative powers. Disturbance of the integrity of the skin by a chronic dermatitis or other eruption may however rapidly lead to the establishment of an abnormal bacterial flora which contains many pathogenic or potentially pathogenic organisms We would emphasize, therefore, the extreme importance of avoiding any irritating or sensitizing medication in the treatment of skin diseases, because when reactions to such substances occur pathogenic bacteria are encouraged and the problem of treatment is complicated.

(2) With a moderate injury such as a scratch or cut there is little likelihood of infection of the skin from bacteria already resident in it because benign organisms are overwhelmingly in the majority and the skin is thoroughly accustomed to living with them In fact, it is possible that some of these organisms contribute in a positive way to the maintenance of the health of the skin.

(3) After an injury to the skin the only source of pathogens which need be seriously considered are bacteria which have been introduced from without, or from some focus within the body such as the nasopharynx or the gastro-intestinal tract These represent transient organisms and they are easily removed by washing unless the injury is penetrating and inaccessible. For this reason it is logical to treat such injuries initially by thorough cleansing with soap and water and not through the application of various antibacterial agents Agents such as mercurial compounds and iodine are of unproven value *in vivo* in respect to antibacterial effects, and have a capacity to produce irritation and death of tissue or sensitization and are therefore sometimes harmful We do not believe that many of the ordinary household first-aid topical remedies for cuts and scratches have any firm scientific basis.

(4) The maintenance of relative dryness of the skin is of extreme importance in preventing pathogenic organisms from gaining a foothold during the healing of a wound or during the course of an acute dermatitis This is abundantly clear from much experimental and clinical evidence. Furthermore there is no indication that infection occurs from airborne contaminants with any regularity It is

our policy therefore, to expose such areas to the air as much as possible and, particularly to avoid the application of occlusive dressings which may become soggy from serum, perspiration, or water

(5) A further source of moisture is through sweating. There is the added complication of sweat-duct obstruction which invariably occurs as the result of any moderate injury to the skin, or from any dermatitis. The best, indeed the only method of preventing this is to reduce sweating by keeping the patient in as cool an environment as possible. This is of particular importance, in our opinion, in the treatment of infants, who are often maintained, to their detriment, in an artificial tropical environment.

(6) It is of the greatest importance to recognize acute secondary infection of a dermatitis as quickly as possible, and to treat it adequately If the infection is allowed to run unchecked for several days or weeks, the responsible organism may become firmly established as part of the resident flora.

(7) If an area of chronic dermatitis or other eruption has become chronically infected with pathogenic bacteria, it is practically impossible to dislodge these bacteria unless the integrity of the skin is returned to normal. Even then the pathogenic bacteria may be recoverable from the area for very long periods.

(8) If it is considered advisable on clinical grounds to undertake antibacterial therapy in the treatment of dermatitis or eczema, careful bacteriologic study is often well worth while. Study by the smear technique as outlined on page 199 is suggested. If cultures are taken, every effort should be made to determine which bacteria are chiefly responsible for the infection noted, and the respective sensitivity of these bacteria to various antibiotics determined It is not considered advisable simply to use a succession of antibacterial agents externally or internally this represents a type of shotgun therapy which may have definite recoil effects in terms of sensitization of the patient, and of increasing the resistance of bacterial strains to certain antibiotics.

(9) The methods of determining the clinical significance of sensitivity to bacteria recovered from dermatitic skin are unsatisfactory Nor is it clear that attempts at producing hyposensitization by the injection of vaccines or denatured toxins have any regular good effects. Indeed, the effects at times may be harmful.

(10) The general tendency to regard chronic otitis externa as a fungus infection is unfortunate. True fungus infections of the external ear are rare. The application of antifungal preparations will, therefore, not be effective. If they are irritating, such treatment will do harm. It is of importance to determine whether or not the external otitis is related to middle ear disease, or is a localized expression of dermatoses such as seborrhoeic dermatitis, eczematous contact dermatitis, psoriasis, neurodermatitis, or apocrine gland retention syndromes.

(11) In the treatment of any cutaneous infection, it would appear that the following general rules may apply on the basis of present evidence.

(a) It is of the greatest importance to avail oneself of every measure to make the skin as inhospitable as can be to the pathogenic bacteria. These factors have been mentioned above and include dryness, avoidance of mechanical or chemical irritation in so far as possible proper treatment of the underlying dermatosis, and avoidance of topical sensitizing medication.

(b) Cleansing and degerming of the skin by simple measures is fully as important as any specific antibacterial medication, if not more so. Soap and water and

compresses of bland character are of great assistance If desired, washing of the area with a soap substitute containing hexachlorophene may be useful. With simple measures such as this some 75–80 per cent of primary superficial infections of the skin may be overcome within a week unless there is some complicating factor

(*c*) In the use of topical antibacterial agents it is our general policy not to subject the patient to the risk of sensitization to a compound which he may require later for the treatment of some serious internal infection On the basis of this rule, substances such as sulphonamides, penicillin, and streptomycin are never employed. We also do not use terramycin and aureomycin externally From our own experience, it would appear that erythromycin may be a fairly potent sensitizer when applied topically and we do not use it Moreover it is a valuable antibiotic when administered internally especially to patients with infections by bacteria resistant to penicillin

(*d*) Bacitracin neomycin and gramicidin are all excellent antibiotics, apparently possess a low capacity to sensitize the skin and will rarely if ever be used internally Bacitracin alone is useful but will not affect enough of the bacterial strains found on the skin. At the present time, we would regard preparations containing both bacitracin and neomycin as reasonably safe, and as having a wide enough spectrum of antibacterial effect to yield extremely satisfactory results. In the treatment of acute otitis externa, the addition of polymyxin may be advisable to overcome the predominant infection with pseudomonas

(*e*) It should be clearly recognized that topical antibacterial therapy has serious limitations, unless the infection is very superficial In processes in which there is gross infection within the skin appendages the antibacterial agent must be administered internally Moreover the vehicle of application is of importance. Compresses are sometimes more effective than ointments. Penicillin is helpful less frequently than was the case five years ago The wide, indeed at times careless, administration of this antibiotic has increased the number of penicillin resistant strains of bacteria, and has sensitized many patients to this valuable compound.

(*f*) It is of importance to realize that correct surgical principles of drainage apply as fully to the skin as elsewhere. Our experience has shown repeatedly that antibacterial therapy alone is not sufficient unless abscesses, even very small ones such as might occur with folliculitis are drained mechanically

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CHAPTER 12

ALLERGY IN RELATION TO DERMATOLOGY

DAVID HARLEY

INTRODUCTION

THERE are few branches of medical science which are more burdened with conflicting theories and speculations than that of allergy Some of this confusion is due to the multiplicity of terms used for the various types of allergic phenomena and to the different interpretation of the same term by pathologists and by clinicians. It therefore seems desirable to provide definitions of the terms employed, before they can profitably be used in discussion because the successful clinical application of the techniques of allergy in diagnosis and in therapy depends upon a clear understanding of the fundamental principles involved. The following classification is not claimed to be a complete one, but it has the merit of relative simplicity and has been found convenient, helpful and generally acceptable by allergists

Though allergy" was originally defined by Von Pirquet as "the altered capacity for reacting which follows disease or treatment with a foreign substance" the term has been extended to include *all types of specific hypersensitivity and it may* be defined in the broad immunological sense to cover all forms of specific increased reactivity in man and the lower animals which are mediated by abnormal or special mechanisms, irrespective of whether these conditions are spontaneous, acquired or induced This definition excludes intolerance" which is due to a quantitative increase of normal physiological response. For example, a patient who after an average dose of aspirin gets tinnitus and deafness is said to be intolerant because the condition is an exaggeration of the normal pharmacological *action of the drug but another patient who after a small* dose of the same drug develops asthma or urticaria, is said to be allergic, because the reaction is qualitatively abnormal is believed to be mediated by a special mechanism and is often dramatic in its intensity having regard to the minute stimulus applied

At least five main sub-divisions of allergy have been recognized, and these are clearly separable from one another in respect of their aetiology pathology or immunology

TYPES OF ALLERGY

Anaphylaxis

Anaphylaxis may be defined as that form of hypersensitivity—readily demonstrable in the lower animals—in which the sensitive state is not spontaneous, is not influenced by heredity is readily induced in the majority of individuals of the susceptible species, and in which an antigen-antibody reaction has been demonstrated. Contrary to popular opinion anaphylaxis has not been conclusively demonstrated in man So-called anaphylactic shock in man is usually allergic shock (hereditary allergy group).

Hereditary allergy group

In this group are included those forms of hypersensitivity in man such as asthma, hay-fever urticaria, eczema, and others, which appear spontaneously in a small percentage of the population, have never been induced experimentally and which are subject to hereditary influences. They are characterized by positive skin-reactions of the immediate "wheal-and-erythema" type, and the chief pathological basis of their manifestations is spasm of smooth muscle and increased permeability of blood capillaries. The clinical variations in this group are considered to be due more to the route by which the specific reaction-exciting substance (which is called the *allergen*) gains access to the sensitized tissues (known as the allergic *shock tissues*) and to the varying degrees of sensitivity of these tissues, than to any fundamental immunological differences. Thus in any one of the clinical types, the injection of the specific allergen may produce asthma, rhinitis and urticaria simultaneously as occasionally happens in hay-fever if an overdose of pollen extract is accidentally given in the course of desensitization treatment.

There is also a close clinical relationship between the various manifestations in the group. Two or more may occur in one patient, the attacks commonly alternating, as for example, rhinitis and eczema, or in co-incident bouts of, say allergic conjunctivitis and asthma or one condition may be replaced by another member of the group, so that an infantile eczema may give place to childhood hay-fever perhaps only itself to be followed by asthma in adult life.

Generally speaking the allergens concerned in this group are of protein nature and include bacterial products. The shock tissues involved are mainly the upper cutis, mucous membranes, and bronchial and certain other smooth muscle.

The reaction of the allergic skin to the specific allergen is similar to the reaction of the skin to histamine, and it is believed that the interaction of the allergen with the specific allergic antibody liberates preformed histamine (known to be present in the allergic shock tissue) from the tissue cells, and that it is thus released histamine which in turn produces the spasm of smooth muscle and increased permeability of capillaries which constitute the allergic reaction. The release of histamine by the cells is the result of cellular damage, and the allergic reaction is simply the expression of cellular damage produced by special method of allergen–antibody union.

The accumulated evidence of more recent work strongly supports the histamine concept, and although there is some indication that not every manifestation of allergy can be explained on the basis of histamine activity it does confirm that histamine is the major factor involved.

Allergic contact dermatitis

In allergic contact dermatitis the sensitization is of the acquired type, being uninfluenced by heredity and occurs predominantly in adults, affecting men more frequently than women. Both the age incidence and the sex incidence are probably the result of increased exposure to occupational allergens. The shock tissue is the epidermis the diagnostic test is the patch test the reaction is an erythematous or vesicular dermatitis and the histopathology is spongiosis and intra epidermal vesiculation. The immunological mechanism of allergic contact dermatitis is unknown.

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the specific infective characters of the organism. Since there are no micro-organisms closely related to the tubercle bacillus which commonly infect man the tuberculin reaction and the allergic aspects of tuberculosis are both characteristic and specific.

On the other hand, when we consider organisms such as streptococci, which commonly inhabit man both as commensals and pathogens, we find that the allergic characteristics tend to belong to the species of organism rather than to the type. It cannot be too strongly emphasized that the allergic response is determined by the biochemical nature of the antigen or allergen, from whatever source it may be derived. Thus among the pneumococci the allergic reaction to the capsular carbohydrate fraction of the organism is type-specific, the allergic reaction to the nucleoprotein fraction is species-specific, while the response to the intact heat-killed organisms is also induced by the viridans streptococci. It follows that when immunity and allergy are determined by the same aspect of an organism, they are likely to be related to one another, but when there is no identity of causal derivative this relationship will not be found. There can thus be no broad identity between bacterial allergy and antibacterial immunity.

Serum disease and drug allergy

Serum disease

When normal (non-allergic) individuals are injected with a *foreign* serum, various reactions known as "serum disease" may develop, depending on the amount of serum given and on the route of administration. If a large dose of whole serum is given intravenously nearly all individuals will develop serum disease. The incidence falls as the dose is reduced and slower absorption routes are used; refined fractionated sera are much less prone to induce the disease than whole natural sera. There are two distinct types of serum disease.

"Ordinary" serum disease.—This disease commonly follows a first injection of foreign serum after an interval of 6–14 days, and consists of various degrees of one or other of a range of skin eruptions (commonly urticarial, but may be scarlatiniform, rubelliform, petechial, and others) with or without pyrexia, angioneurotic oedema, joint pains, serous effusions, and enlargement of spleen and lymph glands. Skin reactions are negative, there is no indication of any hereditary factor, and though the precise immunological mechanism is not definitely established there is some evidence to suggest that an antigen-antibody reaction is involved. Of the sera available, horse serum is one of the most potent inducers of serum disease, and bovine serum one of the weakest.

"Accelerated" serum disease.—This form of serum disease may occur in persons who have previously received one or more injections of serum of the same animal species. The condition—which tends to be a more accentuated form of the "ordinary" disease—develops more rapidly and may be severe. Precipitins, anaphylactic antibodies, and sometimes allergic antibodies are demonstrable in the blood; positive skin reactions may be present. Though, as in the "ordinary" type, the immunological mechanism of the "accelerated" disease has not been fully established, the condition does appear to be a form of acquired specific hypersensitivity. Of all types of human allergy this seems to be the nearest to the classical anaphylaxis of the lower animals.

There is a third type of reaction to an injection of *heterologous* serum, namely

The allergens causing contact dermatitis are commonly of occupational origin, and include vegetable, animal and chemical substances Many of these allergens have been shown to be substances of low molecular weight, water soluble or oil soluble, not of protein nature or even associated with proteins. Whereas many substances such as phenol caustic alkalis and acids, or physical agents such as heat and friction by their irritant action on the skin, are capable of producing dermatitis, this is *not in any sense an allergic reaction. Allergic contact dermatitis*, on the other hand is produced in individuals sensitized by previous contact by substances which are harmless to the skin of normal unsensitized individuals. That the capacity to become sensitized through skin contact is acquired and not inherited is shown by the comparative ease with which normal individuals can be sensitized experimentally by treating the skin with potent sensitizers, such as primula or poison ivy It is impossible to define sharply the borderline between these two groups of dermatitis—the primarily toxic and the acquired sensitization —and in many cases both factors may be involved

The normal epidermis has several protective barriers—the existence of the horny layer the ability to neutralize acids and alkalis, and the presence of fatty sebaceous secretions. It has long been recognized that certain types of skin, such as the abnormally dry moist or oily are more prone to sensitization, as are skins which have been exposed to the action of irritants, such as caustic alkalis, or to mechanical trauma or maceration or which are the seat of fungus or microbic infections

On the clinical side there has been much confusion concerning the use of the terms eczema and dermatitis The majority of allergists have limited their use of the term eczema to those inflammatory conditions of the skin occurring principally in individuals with a family or personal history of allergic disease, which are the results of intrinsic causes of a haematogenous nature, whereas the term *dermatitis, or rather* allergic contact dermatitis, has been reserved for those allergic dermatoses caused by external irritants, and which are not subject to hereditary influences It is in this sense that the terms eczema and dermatitis are here employed Recent work has shown that this aetiological differentiation is supported by consideration of their *pathological and immunological mechanisms*, and *by the different test methods* required for their specific diagnosis

Bacterial allergy

Bacterial allergy or *hypersensitivity* accompanying infection as it used to be called, is now known to be produced not only by the activity of living bacteria in the body but also by the administration of dead bacteria and certain of their derivatives. The test is the intradermal the shock tissue is the cutis and upper cutis, and the response is essentially an inflammation

Within this group there are several separate and distinctive *immunological* mechanisms involved The pathological basis of this group of conditions is *generally an inflammation and is not limited as to site* of lesion or tissue affected Tuberculin allergy is the typical example. Since, however bacteria may give rise to products as diverse as nucleoproteins and carbohydrates an allergic response appropriate to any such products may be produced The immunological mechanism in this group is determined by the biochemical nature of the bacterial product producing the sensitization and is not *necessarily related in any way to*

phenomena are usually side accompaniments of a more systemic infection, for example the tuberculin reaction.

This is an aspect of the subject which is of great importance in treatment though it does not always receive from clinical allergists the consideration which it undoubtedly merits.

The older theory of bacterial toxaemia or focal sepsis, which was based on the conception of a primarily toxic action of bacterial products elaborated in the focus, has been found to be untenable in the majority of cases of these conditions classified as bacterial-sensitizations.

If the matter be considered from the standpoint of allergy and if the processes involved are regarded as an allergic sensitization to bacterial products and not as a primarily toxic effect, many of the objections to the older bacterial toxaemia theory are removed. The chief objections to the bacterial toxaemia theory were, first, the failure to achieve good results by surgical means in the majority of cases in which a localized focus—capable of removal—was found, and second, the failure to find in many cases an infective focus at all. The relative failure of surgery in this type of case may sometimes be due to incomplete removal of the focus, but the main reason is probably an immunological one. If the mechanism is regarded as an allergic reaction to the nucleoprotein or endotoxin of the organism concerned, the matter takes on quite a different complexion. Bacterial nucleoproteins are not type-specific (those of the pneumococci and viridans streptococci are not even strictly species-specific) so that a considerable degree of immunological overlap exists. Now when dealing with those species of organisms which commonly inhabit man, both as commensals and pathogens, it does not follow because, say a streptococcal focus in the tonsils is removed, that the supply of nucleo-protein allergen to the site of the allergic reaction is completely cut off, because other types of streptococci with similar nucleo-protein may be present in other parts of the body for example in the nasopharynx and may be able to keep the reaction going. The problem therefore, would seem primarily to be one that calls for an attempt to readjust the patient's abnormal reactions back towards normality. We may note here that antibiotics are often unavailing in the treatment of bacterial-sensitization allergies.

While the surgical removal of a focus may be a desirable thing, it should not for the foregoing reasons be usually more than complementary to the appropriate desensitization treatment.

Regarding the second objection to the bacterial toxaemia theory namely the failure to find a toxic focus, this should be regarded as primarily a matter for the bacteriologist, since a toxic focus does not necessarily entail the presence of diseased tissue, or of clinical signs of an acute or chronic infection, and accordingly ordinary clinical diagnostic methods are likely to be inadequate.

Urbach (1946) has called attention to the importance of one form of toxic focus which has received only scant attention, since it may show no local signs whatever namely pathological flora of the intestine, particularly the colon. This condition (originally named "colon dysbacteria" by Nissle (1936)) is characterized by a replacement of the normal colonic flora by streptococci and atypical colon bacilli. In the writer's opinion, such pathological flora of the intestine frequently constitutes a toxic focus in bacterial-sensitization cases.

Failure to discover toxic foci is the failure of the bacteriologist. Routine

allergic shock This occurs in persons who are naturally allergic (hereditary allergy group) to the particular species of serum and in whom the skin reactions are positive The immunological mechanism is an allergic reaction, and the condition is usually severe and may be fatal

Drug allergy

Drug allergy bears a close resemblance to serum disease, and for this reason it is included in the group As was pointed out at the beginning of this chapter allergy to a drug is quite distinct from the condition of intolerance, because the reaction induced by the administration of the drug to the hypersensitive individual is qualitatively abnormal and is not merely an exaggeration of the normal pharmacological action Drug allergy can occur in respect of almost any drug, and the skin manifestations of the condition may take almost any form. The drug may be given by any route, and the "incubation" period may vary from a few hours or less to a number of days Skin tests are usually negative, the condition is acquired there is no evidence of a hereditary factor and the precise immunological mechanism is unknown

Other types of allergy to drugs do of course occur—for example, in allergic contact dermatitis, and drugs may function as allergens in the hereditary allergy group—but these are more conveniently considered under their respective allergy groups. In the former the skin tests (epidermal or patch) are often positive in the latter skin tests (dermal tests) are almost invariably negative though positive skin reactions in patients clinically hypersensitive to the various sulphonamides have been reported by using as test allergens the sera of other individuals receiving sulphonamide therapy Presumably the drugs act as haptenes and require to be linked with some human protein in order to achieve full allergenic activity

ALLERGY TO INTRINSIC BACTERIAL ALLERGENS

In practice one is impressed by the frequency with which allergic dermatoses appear in association with some form of infective process, and in which the clinical and laboratory evidence suggests that the relationship between the infective process and the dermatosis is one of cause and effect. The results of therapy based upon this aetiological concept give considerable support to the hypothesis that the infective factor is the cause of the allergic manifestation, though the precise nature of the mechanism involved is not always clear Further the use of skin tests with bacterial vaccines and extracts has proved relatively unsatisfactory as a diagnostic measure in sharp contrast to the reactions obtained with extrinsic allergens in patients sensitive to contactants, inhalants and foods.

The writer employs the term bacterial-sensitization for all those types of allergic disease in which the allergen appears to originate from an infective process, which may be either at the site of the manifestation of the allergic condition—as respiratory tract infection in the causation of rhinitis or asthma—or at a distance from it and the allergen conveyed to the shock tissue usually by the haematogenous route —as when an intestinal infection produces eczema, or a dental infection causes urticaria. In this sense, of course, the term "bacterial-sensitization" is not synonymous with the more classical "bacterial allergy" in which the allergic

in the clinic). Since the amount of trauma inflicted on the skin by the prick method is much less and more constant in degree than in the scratch and intradermal methods, doubtful and pseudo-reactions are much less frequent further the danger of general reactions, by no means negligible with the intradermal method, is reduced to a minimum. The writer has only once seen a general reaction following a prick test, and that was a very mild reaction in a patient exceedingly sensitive to grass pollen.

Technique of prick-testing.—All-glass or tuberculin syringes fitted with No 15 short hypodermic needles are employed. A small quantity of the extract to be tested is drawn into the syringe and a drop is ejected on the patient's skin (the fore-arm, arm, or front of the thigh are usually the most convenient). Holding the syringe pen-fashion the skin is lightly pricked once with the needle, through the drop, at right angles to the surface. The drop of extract is then gently wiped off with a pledget of cotton-wool. Control tests with normal carbol-saline solution and with a solution of histamine are included with each set of tests. The optimum depth of the puncture is about ½–1 millimetre, that is just sufficient to be felt as a definite prick, the process is not painful and blood need not be drawn. The reactions are read after 10 minutes. Comparative tests have shown that increasing the depth of the puncture so as to produce an unpleasantly sharp sensation and draw blood is without much effect on the size of the ensuing reaction.

The chief essential for the satisfactory performance of the prick test is the use of potent concentrated fluid extracts, which usually have a concentration of not less than 10 per cent that is, 1 gramme of substance treated with 10 millilitres of extracting fluid (or 100,000 units per millilitre on the Noon unit system) in the case of weaker allergens like fruit and vegetable juices more concentrated extracts are needed. The most potent and satisfactory extracts are usually those prepared with the minimum of chemical and physical manipulation. The keeping properties of these extracts vary but the average loss of potency after one year in the ice-chest is not usually more than 25–30 per cent with the majority of extracts, as judged by comparative skin tests. It is therefore advisable to renew the stock supplies at least once a year

Interpretation and significance of positive reactions.—There is usually no difficulty in deciding the degree of reaction of the skin to any allergen compared with that to the control carbol-saline solution, as tested by the prick method. With the technique described above the size of the reaction to a particular allergen is remarkably constant. The results of the prick method are very readily assessed as strong positive positive weak positive and so on. By any technique there is never any doubt about a strong positive, but with regard to slighter degrees of reaction the prick method gives more uniform results than do the scratch or intradermal methods. The accuracy of assessment of the degree of reaction, especially when dealing with weak reactions, depends on the absence of appreciable non-specific irritant effect of the extract used, and all extracts should be tested in normal non-allergic skins before being employed as specific test reagents. Except in dermographic skins, non-specific reactions are rare with the prick method, in view of the very slight and constant trauma inflicted on the skin and of the very minute amount of test fluid deposited in the *cutis vera*.

The assessment of the clinical significance of a positive reaction is a much more difficult matter A positive reaction may mean that the patient is clinically sensitive to the particular substance when met with in the natural manner or is not clinically sensitive, though he may have been sensitive at some time in the past or

determinative bacteriological methods for the detection of toxic foci in those cases in which the causal mechanism is a bacterial-sensitization, are of little more use than would be the employment of toxicological methods in a case of food allergy In neither case are we looking for a primary toxin but for an abnormal reaction on the part of the patient. In bacterial sensitization the use of bacterial vaccines extracts and solutions for skin tests has proved relatively unsuccessful. This may be due to our inability to prepare suitable bacterial allergens for the purpose of the test, but the main reason is probably the relative lack of specificity in sensitization to bacterial nucleo-proteins.

Fortunately another technique is available for tackling the problem from a different angle. This is the method of pathogen-selective culture, which is discussed later (p 224) In the writer s experience this method for the detection of toxic foci and for the preparation of bacterial antigens for therapeutic desensitization is extremely valuable, and would appear to be the only rational method at present available.

SPECIFIC DIAGNOSIS

As in all other allergic diseases, a careful examination of the clinical history with particular attention to the correlation of the attacks with occupational or other pursuits with seasonal and other factors, with the use of medicaments, is of prime importance as the first step in the specific diagnosis The location of the initial lesion is often of value in determining the importance of possible allergens.

It is necessary to ascertain the substances with which the patient comes into contact either occupationally or otherwise, by careful questioning and by reference to the available lists of known excitants encountered in the various trades and occupations Consideration of the foregoing aspects of the case will often narrow the search to a relatively small group of substances, and will thus aid in the selection of substances for skin testing

Skin tests

Dermal tests

The well known diagnostic tests of the wheal-and-erythema type are generally applicable in the hereditary allergy group (asthma hay-fever eczema urticaria). As the shock tissue involved in this reaction is the blood vessels of the upper cutis, the epidermis must be penetrated to allow the allergen to reach the sensitized cells. There are three main techniques for the test. (i) The *scratch* method which consists of scarifying the skin with a needle or scalpel and applying the allergen solution or powder (ii) the *intradermal* method which consists in the injection of a small volume of the allergen solution into the dermis by a syringe fitted with a fine short-bevelled needle and (iii) the *prick* method, which consists in pricking the skin with a needle through a drop of concentrated allergen solution this technique was originally introduced by Lewis (1924) in his classical studies of the reactions of the skin to histamine, as the only method capable of giving precise quantitative results, and has been applied to the diagnostic skin testing of allergy patients.

For routine use the advantages of the prick method of testing over the scratch and intradermal methods are simplicity accuracy almost complete absence of discomfort to the patient and rapidity of performance (the last being a very important point when dealing with children and with large numbers of patients

of a circumscribed area of inflammation, varying from erythema in the case of mild reactions to vesiculation with necrosis in the case of powerful allergens, and it often reproduces the type of lesion present in the patient.

Although the patch test has been established on its merits as a valuable diagnostic aid in allergic contact dermatitis, it is subject to the same limitations as those governing the dermal tests in other types of allergic disease, and the results must be interpreted with care and with due respect to the other aspects of the case.

Clinical trial

This method can be applied in two ways (i) as a confirmatory test that the allergen—suspected from the results of skin tests or otherwise—is the cause of the natural disease, by obtaining improvement or disappearance of the dermatitis when the substance is withdrawn from contact with the patient (which may require several weeks) and (ii) to detect the causal allergen or allergens in the absence of positive skin reactions. For example, a patient with cosmetic dermatitis, after a period of avoidance of all cosmetics with clearing of the rash, tries each of the possible excitants for a week or so in turn in order to determine which one of the suspected agents is responsible. Similarly elimination diets are often of great value in the investigation of cases of suspected food allergy

Bacteriological methods

It is well-known that even in cases of chronic or focal infection which are recognized clinically it is often a matter of great difficulty to pick out the causal infecting organism from the numerous secondary invading organisms and non pathogenic bacteria which are usually present

In our problem the bacterial products which have sensitized the skin have necessarily travelled to that tissue by the blood stream. It is therefore, reasonable to suppose that the test of surviving exposure to the patient's own fresh whole blood might be a valuable method for the elimination of irrelevant bacteria.

This approach is of general application, and under one name or another is widely used by the old hands in the realm of clinical bacteriology It was originally described by Solis-Cohen and Heist in 1921 under the name "pathogen-selective" culture, and was independently reported a little later under the name of "autohaemoculture by that doyen of British immunologists, the late Sir Almroth Wright.

It has been generally agreed by immunologists that the virulence of bacteria for an individual, and the degree of the individual's resistance to the bacteria, depend upon the ability of that individual *to remove the bacteria* from his blood stream an ability which is reflected in the *in vitro* bactericidal power of his freshly drawn unclotted blood, first demonstrated by Fodor in 1887

The principle of the pathogen-selective culture is the utilization of the *in vitro* bactericidal power of the patient's whole fresh blood to kill off organisms to which he is immune and to allow the growth of potentially pathogenic organisms, thus assisting in the selection of the aetiologically important organisms from a mixed culture in cases of chronic or focal infection.

The essential feature of the pathogen-selective culture is the use of freshly taken unclotted blood. It is, therefore, desirable that the clinical pathologist should

may be about to develop such clinical sensitivity Occasionally a reaction may occur to a substance which could not be responsible for present or past sensitization or even to a substance with which the patient has never been in contact, for example an Englishman who suffers from hay fever may react to the pollens of the bamboo and the sugar cane. Most of these reactions are due probably to biological relationships between the allergens in question but occasionally they may be due to chemical similarities in biologically unrelated substances, akin to the precipitin reaction between type 2 anti pneumococcus serum and certain hydrolysed gums, which is caused by similarities of the carbohydrate groups of the hydrolysed gums and the type 2 pneumococcus. In this connexion also it is well known that practically every person who has previously received animal serum for therapeutic purposes exhibits a positive skin reaction to that serum but a person thus sensitized to say rabbit serum does not develop allergic symptoms on natural contact with rabbit fur or rabbit meat

A negative skin reaction may mean that the patient is not clinically sensitive to the substance, is clinically sensitive in the absence of skin reactions, or that the extract used is not potent.

As a general rule, however it is to be emphasized that the importance of any allergen as a specific causal factor in an allergic disease should not be adduced from a positive skin reaction alone. A positive reaction is rarely of much help as a clue to the specific diagnosis and treatment in the absence of evidence of a corresponding clinical sensitivity obtained from a study of the clinical history It is the correlation of skin reactions with clinical sensitivity that is the basis of accurate specific diagnosis and successful treatment. Although skin testing is admittedly the most helpful single specific allergic diagnostic technique at our command, it must always be a complement to and never a substitute for the trained clinical judgment in the field

Epidermal tests

The patch test was introduced for contact dermatitis many years ago by Jadassohn (1894) but it did not attract much attention until comparatively recently when the demonstration that the epidermis and not the cutis is the shock tissue (site of primary lesion) in contact dermatitis led to its development The principle of the test is the establishment of prolonged contact between the suspected allergen and the non-abraded epidermis

Technique.—In the case of solids, a small portion of the powdered substance (which may be moistened) is placed directly on the skin in the case of fluids, a small square of linen, gauze, or filter paper soaked with the fluid is used The site is then covered with a larger square of cellophane or oiled silk, which is held by means of an over lapping square of adhesive tape. It is advisable to include a control test of cellophane or oiled silk with adhesive tape in case the patient is sensitive to these Generally speaking, it is best to test on areas of skin fairly close to the dermatitis area, or on sites which have been involved in previous attacks, although many workers routinely employ the skin on the back The patches are left *in situ* for 24–48 hours, unless marked itching or a spreading rash demands their earlier removal In the case of dress materials, and such like, it is often necessary to leave the patch for 7–10 days before a reaction develops. This is probably due to the fact that the element of friction often active in the natural induction of the dermatitis, is not duplicated by the method of testing, so that more prolonged contact is necessary A positive reaction consists

enhance the antigenicity of the histamine hapten. Preliminary immunological and animal tests were encouraging, but the results of clinical trials have not fulfilled expectations.

Specific avoidance

When the clinical sensitivity is to a single allergen or to a small number of allergens, which can be readily and completely removed from contact with the patient, specific avoidance gives excellent results. This can usually be achieved in most cases of food and drug sensitization. The method is also generally applicable to all contactant and inhalant allergens which are relatively localized in their distribution and can be completely avoided or eliminated from the patient's environment without serious inconvenience or hardship. In other cases, an easier alternative may be the removal of the patient from the causal environment.

When such avoidance of contact would entail serious financial or other hardship, as, for example, in many cases of occupational allergy, much can sometimes be accomplished—after a period of complete avoidance and subsequent clearing of the dermatosis—by reducing further contact to the minimum by appropriate protective measures.

When avoidance is impracticable or impossible there remains desensitization to be considered.

Desensitization

Broadly defined desensitization consists in the application of immunological therapeutic methods to render the tissues of the allergic patient less sensitive to the causal allergen, so that he will then tolerate natural contact with the offending substance without developing the allergic symptoms. Theoretically such clinical desensitization may be achieved by either non-specific or specific immunological methods.

Non-specific

The technical difficulties of specific methods of clinical desensitization stimulated the early allergists to seek therapeutic short-cuts and, chiefly as the result of wishful thinking, there was born non-specific desensitization—a process to desensitize any allergic patient without troubling to find out to what he is allergic.

Many of the methods of attempted non-specific desensitization have employed shock tactics in the hope that an induced acute immunological reaction *in vivo* might favourably influence the patient's specific sensitivities, for example, the injection of typhoid vaccine and milk protein. Some methods have sought to obtain the autogenous though unidentified allergens, for instance auto-haemotherapy and the ingenious but ill-fated urinary proteose, whilst others have tried to get a more universal effect from peptone, tuberculin, ethylene disulphonate, and various histamine preparations. None of these methods has proved to be regularly effective, and many have fallen into complete disuse. Of the survivors, tuberculin, TAB, and histamine are perhaps the favourites, although their employment is rather a confession of failure in making a specific aetiological diagnosis, and their use is generally confined to a group of doubtfully allergic dermatological conditions of unknown specific aetiology which are not amenable to other forms of treatment.

himself carry out the examination of the patient and the collection of the various specimens in the laboratory

In practice it entails making a series of cultures from tonsils, faeces, urine, and so on, in the medium of the patient's own blood and the results of these cultures are compared with a series of ordinary direct cultures prepared on the appropriate routine culture media.

Technique of pathogen-selective culture.—A small amount of the infected material is placed in a sterile 4 × ½ inch test tube, to which is then added 1–2 millilitres of the patient's whole fresh blood (venous) In the case of heavily infected material, such as sputum and faeces, it is better to make 3 or 4 serial dilutions of the material in blood ("fractional" pathogen-selective culture) in case the primary implant would prove too heavy The tubes are incubated at 37° C. for 24–48 hours. Subcultures are then made on to blood-agar and other suitable media and incubated The resulting growths are examined and compared with a control series of direct cultures of the pathological material.

Vaccines are then made of the pathogen-selective positive micro-organisms, that is, those organisms which survive the bactericidal power of the blood and grow in the subcultures made from the incubated mixture of blood plus pathological material. In normal persons such pathogen-selective culture from, say a tonsil swab will result in negative subcultures, that is, the blood kills all the organisms present (pathogen-selective negative culture) Similar cultures in urticarial patients provisionally diagnosed as bacterial-sensitization allergy from an upper respiratory tract focus, will commonly select one of the various micro-organisms present on the tonsil, and the pathogen-selective positive culture will contain a heavy pure growth of that particular organism (Repeat tests at intervals will regularly give precisely similar results.)

THE THERAPEUTIC CONTROL OF ALLERGY

All rational therapeutic methods are based on the attempted interruption of some phase of the allergic reaction

Specific avoidance aims at preventing contact between the causal allergen and the allergic shock tissue. Desensitization, specific and non-specific, attempts to *render the cells of the shock tissue insensitive to the action of the allergen.* Allowing the allergen-antibody union to take place, attempts can be made to *modify the action of the liberated histamine* There are a number of possibilities here (1) *It can be blocked by the use of the antihistamine drugs* though the effect is, of course, only temporary (2) drugs which have a pharmacological action the reverse of that of histamine (such as adrenaline and other sympathomimetic agents) may be administered (3) *attempts can be made to neutralize or inactivate the liberated* histamine, for example, by histaminase. This histaminolytic enzyme, discovered by Best in 1929 was found to be quite effective in the inactivation of histamine *in vitro* Nevertheless, apart from favourable reports by a few of the early and presumably over-enthusiastic experimenters, it failed to achieve a therapeutic success, and the treatment has fallen into disuse. Another line of approach to the problem consisted of trying to "immunize" or "desensitize" the body tissues *against* the action of histamine. This was attempted by parenteral and oral administration of graded doses of histamine itself but the clinical results proved disappointing. A more recent development was the introduction of *histamine-azo-protein* compounds, in the hope that the coupling of histamine with a protein molecule would

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Enterococcus vaccine.—Apart from the occasional use of tuberculin, the only non-specific method of desensitization used by the writer with any regularity or much success is the injection of stock enterococcus (intestinal streptococcus) vaccine. This is given by the subcutaneous route in doses of from 250,000 to 10 million heat killed organisms at 4 to 14-day intervals, and also in sub-shock intravenous doses of from 5 to 100 million organisms in patients resistant to the subcutaneous injections.[1] This method has been found useful in a variety of intrinsic allergic dermatosis of probable toxic-allergic or bacterial-sensitization origin, for example, some types of chronic pruritus, urticaria, angioneurotic oedema erythema multiforme, psoriasis, eczema and recurrent dermatitis. The method has been developed as the result of considerable experience in conducting bacteriological investigations by pathogen-selective cultures in similar cases, in which the enterococcus has often been incriminated as of aetiological significance. Further as the species *Streptococcus* provides the great majority of the organisms responsible for all focal sepsis and toxic allergic conditions in man, it seems particularly appropriate to employ as a non-specific desensitizing allergen the intestinal streptococcus—the probable genetic father of all the streptococci.

Specific

The era of specific desensitization was ushered in by the pioneer work of Noon and Freeman in Almroth Wright's laboratory at St. Mary's Hospital during the first decade of the century In 1911 these investigators reported their successful treatment of hay fever by the administration of small subcutaneous injections of a saline extract of grass pollen (Noon, 1911 Freeman, 1911) After the onset of the illness which led to Noon's untimely death from pulmonary tuberculosis at the age of 35 years, the work was continued and developed by Freeman The success and accuracy of Freeman's work on specific desensitization have been confirmed by the universal acceptance of the basic principles which he established, and which have formed the foundation of all modern specific desensitization therapies.

Specific desensitization consists in the administration—usually by parenteral injection—of a graded series of doses of a protein extract of the specific allergen to which the patient is sensitive. The method is generally applicable to all protein allergens of animal and vegetable origin (pollens, house dust animal danders, feathers, moulds, foodstuffs, orris, wool) but it is not, with a few exceptions, practicable when the allergen itself is a toxic or a non-protein substance (drugs, chemicals, antibiotics) Specific desensitization finds its main sphere of usefulness in allergic conditions of the hereditary group—asthma, hay-fever rhinitis, conjunctivitis, eczema urticaria and angioneurotic oedema—and to a more limited extent in contact dermatitis and other allergic conditions

The precise immunological mechanism of specific desensitization is not as yet fully understood It is possible, with sufficient treatment to reduce or abolish both the patient's skin reactions to the causal allergen and the sensitizing antibodies in his serum and also to stimulate the development of special immune or blocking antibodies in his blood But satisfactory clinical results are regularly obtained in practice by a degree of treatment which is insufficient to produce these immunological changes, so the latter do not appear to be essential for clinical cure although conversely clinical cure always does accompany these changes.

Protein extracts for desensitization.—These consist essentially of sterile saline or alkaline-saline protein extracts of the naturally occurring allergenic substances. There is at present no scientific laboratory method for the exact standardization of these extracts—apart from comparative skin testing in the sensitive human subject—so they are usually made up on a weight/volume basis, one unit being the amount of active principle extracted from $\frac{1}{1000}$ milligram of the defatted, dry powdered, parent substance. This unit is usually referred to as the Noon unit, in honour of the originator of desensitization therapy

Route of injection.—The subcutaneous route is generally used and has been proved by experience to be the most satisfactory The intradermal, intramuscular and intravenous routes have been tried at different times, and also oral administration, but they are not to be recommended for general use.

Method of desensitization.—In seasonal allergic diseases there is the choice of three methods of desensitization (i) preseasonal, (ii) perennial, and (iii) co-seasonal.

Pre-seasonal desensitization

Pre-seasonal specific desensitization is undoubtedly the most effective practicable method of treatment at present available for pollen and other seasonal allergies. It consists of a course of graduated injections of the specific protein extract during the 2–4 months preceding the pollen season. The best results are undoubtedly obtained by gradually working up to a massive dose which is sufficient to abolish the patient s skin reactions, so that complete relief of symptoms can be practically guaranteed.

In the previously untreated case it is usually necessary to start with a dose of 20–40 units, increasing by 20 units each time, to a dose of 200 units, after which a 15 per cent increase is made with each successive dose. Experience has shown that this is the most satisfactory rate of dosage increment, if the comfort and peace of mind of the patient are to be considered, and if general reactions to the injections are to be kept to a reasonable minimum. On this dosage scheme a top dose of 5,000 units can be reached in about 30 injections, 20,000 units in 40 injections, and the maximum of 100,000 units in just over 50 injections. The full list of doses (Noon units) for "heavy pre-seasonal desensitization is as follows

40	800	9,300
60	920	10,600
80	1,060	12,200
100	1,220	14,200
120	1 400	16,200
140	1,600	18,800
160	1,840	21,500
180	2,100	24,500
200	2,400	28,500
230	2,750	33,000
265	3,150	38,000
300	3,600	43,500
345	4,100	50,000
400	4,700	57,000
460	5 400	66,000
530	6,200	76,000
610	7 100	87,000
700	8,100	100,000

Dosage and frequency of injections.—The frequency of injections and the top dose to be given, can be varied considerably to suit the individual case and the length of time available for the treatment It is both possible and practicable to work a previously untreated case up to a dose of 100 000 units by daily injections for 8 weeks, although in practice it is often sufficient to aim for a dose of 5 000 or 10,000 units during the first year (giving 3 or 2 injections per week if time permits) and to assess the degree of clinical improvement for the ensuing season, before considering heavier treatment in the second and third year Patients who have received a previous course of treatment may be given an initial dose of 100 units or more, and may tolerate a dosage increment of 50 per cent, slowing down to 25 per cent or so as the bigger doses are reached.

Reactions during treatment—Excessive local reactions are not common with the standard course of treatment detailed above Local reactions form a useful indication of the patient's degree of tolerance to the injections, and should they tend to increase in severity with successive doses, then the rate of increase should be reduced, temporarily at any rate It sometimes happens at some stage of the treatment that the injections produce excessive local reactions. In that event it is advisable to reduce the dose and then to increase again at half the previous rate After the "sticking-point" is passed it is usually possible to revert to the former rate without further trouble. The sticking-point often coincides with some intercurrent ailment or infection or some psychological upset, but for reasons unknown it may occasionally occur at about the same dosage level in the same patient during two consecutive years of treatment.

With the above scheme of dosage general or constitutional reactions, except those caused by accidental overdosage or by leakage into a vein, are comparatively infrequent and are usually mild General reactions can be relieved by the prompt use of adrenaline preferably in small subcutaneous doses (0·1–0·2 millilitre of a 1 in 1 000 solution) at 15 or 20-minute intervals. These reactions sometimes occur at the beginning of the treatment, especially in previously untreated patients, who may afterwards go through the complete course without further trouble. Once the treatment is well under way general reactions of any degree of severity with the standard scheme of doses, given truly subcutaneously are rare in the absence of warning signals from increasing local reactions to the preceding injections

Desensitization in non-seasonal allergies

In non seasonal allergic conditions the type of desensitization treatment to be employed depends to a great extent upon whether or not a temporary period of specific avoidance is possible or practicable. If so a course of pre-seasonal type desensitization can be given, while the patient avoids natural contact with the specific allergenic substance, then changing over to a modified course of perennial treatment when contact is resumed When specific avoidance is impossible, an extended course of co-seasonal type injections is given, and followed by perennial treatment with gradually increasing doses.

Specific desensitization in allergic contact

Dermatitis—Most of the published work on desensitization in allergic contact dermatitis has been on pollen-sensitive and plant-sensitive patients. In accordance with the commonly held view that the causal allergens in these cases are associated with the plant oils, the majority of workers have used for therapeutic desensitization preparations of oil-solvent extracts given intramuscularly or subcutaneously earlier workers having failed to obtain satisfactory results with

aqueous extracts. Other observers, however reported unsatisfactory results with these extracts, but good results with aqueous extracts. In Great Britain Palmer and Freeman (1934) obtained satisfactory results with aqueous extracts in dermatitis occurring in daffodil pickers. The failure of the earlier workers with aqueous extracts may well have been due to inadequate dosage, particularly when it is remembered that the allergen, to effect desensitization, has to reach the epidermis from the blood stream, so that even bigger doses than those necessary for dermal desensitization may be required.

The writer's experience is not extensive, but it indicates that relatively crude aqueous extracts are quite satisfactory. Until the chemical nature of the causal allergens is established beyond doubt, it would seem unsafe to rely on more refined preparations from oil-solvent extracts or otherwise. Specific desensitization has been successfully applied for a range of allergens of animal and vegetable origin. Crude aqueous extracts, prepared by extracting the allergen substance with saline in the presence of toluol at ice-chest temperature and then passing through a Seitz filter are employed. It is, of course, necessary to ascertain by patch tests if the extracts are potent before beginning the treatment. Desensitizing injections of the extract are given subcutaneously starting with a dose of 20 units (Noon system) increasing by 20 units each time to a dose of 200 units, after which increments of 15–25 per cent on each successive dose are made, to a top dose of usually 100,000 units. When there is no special reason for urgency the injections are given at the rate of 2 or 3 per week to start with lengthening the interval between injections to one week as the bigger doses are reached. Whenever possible the patient should practise specific avoidance during the first few months of the desensitization treatment. After the maximum dose is reached, it is repeated at 4-weekly intervals for at least 6 months.

Although the writer's experience of desensitization has been confined to allergens of animal and vegetable origin there seems no reason why desensitization should not be attempted in selected cases of dermatitis caused by more simple chemical allergens. The main drawback to therapeutic experiment in the latter type of case has been the frequency of which the allergen is itself toxic. However the desensitization of atropine-sensitive ophthalmic patients by subcutaneous injections of atropine solution rendered relatively atoxic by admixture with human serum gives a valuable pointer to similar therapeutic trials in allergic contact dermatitis.

Illustrative cases

No. 1 *Wool dermatitis.* Female, aged 28 years. Occupation, nil. Fine papulo-vesicular rash on the upper arms and across the shoulders. Duration, 2 years. The patient was usually free from the rash during hot weather. The distribution of the rash corresponded to skin contact with the woollen jumper which the patient was wearing. She stated that similar garments were regularly worn except during hot weather. There was also a fine branny seborrhoea of the scalp. The general health was good, and there was no history of previous personal or family allergy. Patch tests positive reactions to samples of the patient's jumpers and to wool extract in 10 days negative reactions to wool-fat and control tests. Avoidance of woollen garments for 2 weeks produced a marked improvement but not complete disappearance of the rash. After a further 2 weeks avoidance, together with the application of a salicylic acid-mercury-spirit lotion to the scalp (for the seborrhoea) the rash disappeared. The patient was

desensitized with wool extract during a period of avoidance of woollen garments later return to woollen garments did not cause a reappearance of the rash.

No 2. *Mahogany dermatitis* Male, aged 20 years. Occupation, cabinet-maker Dermatitis of the hands, arms, and occasionally of the face, at intervals over a period of 2 years The patient had noticed that the rash appeared only when he was working with mahogany and quickly cleared up on stopping work Previous personal and family histories were negative for allergy Patch tests with mahogany dust and a saline extract of the dust were positive. The patient was desensitized with the dust extract during a period of avoidance of contact with mahogany at work, and was later able to handle the wood with impunity

No 3 *Rye flour dermatitis* Male, aged 28 years Occupation, baker Dermatitis of the hands and forearms. Duration, 3 years. The patient had noticed that the rash appeared to be associated with his work, especially with rye flour and that it improved or cleared up completely when he avoided contact with rye flour for any length of time. Patch tests with rye flour and with an extract of the flour were positive. The patient was desensitized with the extract continuing at work meanwhile, and he reached a dose of 100 000 units without reactions. The rash slowly improved. The maximum dose was then repeated at 4-weekly intervals for a further 6 months. The rash disappeared and has not returned to date.

No. 4 *Occupational (?) dermatitis* Male, aged 31 years. Occupation, motor mechanic. The patient exhibited typical dermatitis of the hands and arms. There was a history of attacks of a similar rash, sometimes spreading to the trunk, over a period of 3 years The general health was good and there was no previous personal or family history of allergy The patient had been employed in the same garage for 6 years. The first attack had appeared soon after he began to work on Diesel oil engines The rash always improved when he stopped work, but reappeared within a few weeks of resuming, appearing first on the fingers, then spreading to the arms, neck and face and on one occasion when he did not stop work soon enough becoming generalized Patch tests with Diesel oil fuel were negative. Repeat tests were likewise negative. Tests with other engine fluids (lubricating oils, brake fluid) were negative Tests with the soap and cleansers used by the patient were negative. Consideration of these findings suggested that the causal allergen might be associated with the used fuel or oils, that is, the actual material that the patient was getting on his hands during work Accordingly patch tests were carried out with the various dirty fluids encountered in dismantling and adjusting an engine and vehicle. The results of these further tests were uniformly and disappointingly negative.

The clinical history and the appearance of the rash were typical of allergic contact dermatitis The failure to obtain positive patch tests may have been due to a number of reasons—probably the failure to duplicate the actual conditions encountered during work, for example, lack of friction, or to the choice of poorly reacting or possibly refractory areas of skin for the tests, although, of course, the possibility of failure to spot the causal allergen could not be excluded. However the clinical findings and the history seemed to justify the diagnosis of allergic contact dermatitis of occupational origin.

The problem of treatment then arose For economic reasons the patient was loath to consider changing his occupation The use of gloves sufficient for complete skin protection was impracticable. Protective ointments did not appear to offer much hope It was finally decided to try non-specific bacterial vaccine therapy and an autogenous faecal vaccine was prepared After a period away from work, with clearing of the rash the patient was given a course of injections, returning to work later the injections being continued at weekly intervals After 6 months of such treatment the rash, which had slowly returned, is not nearly so acute as hitherto, and the patient has elected to continue at work and to carry on with his injections.

Vaccine therapy

Though some workers have stated their belief that the use of all forms of vaccine therapy in allergic disease must be regarded as non-specific desensitization the writer's experience indicates that desensitization by means of pathogen-selective vaccines is to be regarded as a specific measure and in appropriate cases it gives excellent clinical results.

The dosage with such vaccines must be kept very low otherwise focal reactions will occur though it is often a valuable confirmatory diagnostic test to be able to elicit a temporary focal reaction with a small dose of the autogenous vaccine, before starting the therapeutic desensitization. The best clinical results are generally obtained with the use of minimal doses—rarely in excess of 5 million heat-killed organisms, and usually less—which are given by the subcutaneous route. A starting dose of 0·1–0·5 million, depending upon the nature of the case, is commonly employed The dose is repeated at 4-day to 7-day intervals, and is cautiously increased by 0·1–0·2 million each time until clinical improvement is obtained. The increase of dosage is based on the absence of focal, general, or marked local reaction to the preceding injection. As soon as clinical improvement occurs the same dose, or only a slight further increase, is repeated at 7-day intervals for 2–3 months. Then, if the patient's progress has been satisfactory the interval between injections is increased to 2 weeks, and the dose advanced by about 50 per cent. Later a 3-week or 4-week interval is instituted, with further increase of dose only if necessary for the maintenance of clinical improvement. The injections are continued for a year or longer

In cases of mixed aetiology—commonly a combination of sensitization to inhalant or food allergens, or both, plus an intrinsic bacterial allergy—desensitization with both types of allergens may be combined as the method of choice.

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CHAPTER 13

CROSS-SENSITIZATION PHENOMENA

RUDOLF L. BAER

CIVILIZATION has reached the point where the synthetically made life-saving drug, the essential food factor the clothing dye and the explosive, and many other seemingly entirely unrelated compounds, may be closely related chemically In the event that a person becomes allergic to one of these compounds it is always possible that cross-sensitizations to other chemically or immunologically related compounds will occur These cross-sensitizations or group sensitizations may be difficult or impossible to discover and will be comprehensible only if one is fully aware of the chemical structures of the compounds involved

What is cross-sensitization?

The term cross sensitization is used here to denote the phenomenon where the allergic sensitization, engendered by one compound extends to one or more other compounds Among the other expressions which have been used in the literature to denote the same phenomenon are *group-sensitivity* (Mayer 1929) *cosensitization* (Jausion, 1936) and more recently *coenomerie* and *coeno-sensibilization* (Thulliez, 1952) None of these terms is entirely satisfactory and therefore one might well be tempted to coin a better term. However neither the terms which have been proposed in the literature nor those other new phrases which come to mind constitute a sufficient improvement to warrant replacement of the now generally accepted term, *cross sensitization*

Primary and secondary allergens

Cross-sensitization may be observed under clinical conditions or in the course of skin testing when a specific substance has produced allergic sensitization not only to itself (primary allergen and primary sensitization) but to one or more immunochemically related allergens (secondary allergens and secondary sensitizations). This implies that a substance may be the primary allergen in one patient and the secondary allergen in another For example, in one case the primary sensitization may have been engendered by benzocaine with secondary sensitizations to procaine and para phenylenediamine, while in the next case para phenylenediamine may have been the primary allergen with secondary sensitizations to procaine and benzocaine.

Some compounds, however entirely lack the capacity to *engender* allergic sensitization although they do *elicit* allergic reactions in tissue sensitized by immunochemically related substances The name *elicitors* (Mayer 1949) has been suggested for such substances, and these in an immunological sense correspond to the haptens (partial antigens) of Landsteiner

Theoretically cross-sensitization can be explained by the following possibilities

of an immuno-chemical relationship between the primary and secondary allergens (Baer 1948)

(1) The primary allergen and the secondary allergen are so closely related immuno-chemically (that is, contain identical allergenic groups) that the sensitized cells (that is, the antibodies which are presumably contained in them) do not differentiate between them and thus react towards each as if they were identical (group specificity).

(2) The primary allergen is converted (reduced, oxidized or in other ways transformed) in the body into a compound which is either identical with the secondary allergen or so closely related to it that the sensitized cells do not differentiate between them.

(3) The secondary allergen is converted in the body into a compound which is identical with or so closely related to the primary allergen that the sensitized cells do not differentiate between them.

(4) Both the primary and the secondary allergens are converted in the body into compounds which are either identical or so closely related that the sensitized cells do not differentiate between them.

The allergenic component involved in cross-sensitization may range in size from the smallest to the largest chemical units. In one case it may be an element such as mercury iodine, nickel, chromium or copper in the next a simple, relatively small, molecular grouping in a compound such as an amino-group in the para position on the benzene ring, or a side chain with a tertiary amine. In other cases it may be a large molecular substance such as the identical polysaccharide found in several species of fungi or a very complex long-chained protein either in a group of pollens or in milk or eggs from several species of animals.

The numerous studies on cross-sensitization in which tests were carried out with an extensive series of related allergenic compounds demonstrate the astonishing individuality of the sensitization pattern in each individual patient. In one unpublished series (Furman and Baer) of more than 50 patients with allergic hypersensitivity to para-phenylenediamine, there were no two patients in whom tests for cross-sensitization to 20 related allergenic compounds revealed an identical sensitization pattern. The individuality of these cross-sensitization patterns is comparable to that which has been reported to exist in human fingerprints. Another previously known feature of cross-sensitization was corroborated in this very extensive series of patch tests. The degree of sensitivity to the primary allergen was found to be at least as great, if not greater than to the secondary allergens. Examples will be cited below which prove that there are exceptions, although rare, to this rule.

Examples of cross-sensitization

In patients with clinical evidence of allergic sensitization, but with negative skin test reaction to the causal allergen, studies on cross-sensitization have to be carried out by individual clinical exposures to the many compounds which are to be investigated. This procedure is so difficult and cumbersome that it is impossible to perform in the vast majority of cases. Therefore, careful and detailed investigation of cross-sensitization is usually possible only in those cases and in those forms of allergic sensitization in which skin tests with the allergenic compounds consistently elicit positive skin reactions.

While some examples of cross sensitization are only of theoretical interest, others are of the greatest clinical significance as well. Some patients are sensitive only to the feathers of one species of birds while others have a cross-sensitization to the feathers of several or many species and while some patients are sensitive to the dander of only one species of cats, others have a cross-sensitization to all members of the cat family (lions, tigers, lynxes, leopards and panthers). Among the well-known instances of cross sensitization are those due to group specific allergenic components in the entire group of hyphomycetes, in helminths, in grass pollens in ragweed and pyrethrum and in the many members of the group of rhus plants. It is impossible here to discuss in detail all the known examples of cross-sensitization. The discussion, therefore, will be limited to a few examples which have been studied in *human beings* and which involve only compounds of *known chemical structure* and will take up in more detail the best-studied examples of cross-sensitization—*those found among certain aromatic amines and among* local anaesthetics.

CROSS-SENSITIZATION AMONG ECZEMATOGENIC ALLERGENS

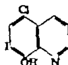
Bruno Bloch (1911) was probably the first investigator who was conscious of the importance of systematic studies of cross-sensitization among simple eczematogenic chemicals. In 1911 he investigated cross-sensitization in iodoform hypersensitivity and observed that the hypersensitivity found in some of his patients who had developed dermatitis due to iodoform was due not to the whole iodoform molecule nor to its iodine content but to the methyl groupings found in this and *other molecules. These studies first revealed that allergic eczematous hypersensitivity* may be due to specific chemical groupings. Later work has shown that in some cases iodoform sensitivity may be based on other characteristics of the iodoform molecule. The hypersensitivity for example, may be directed *towards the* iodine in the molecule, in which case the patient's skin would react to any compound containing iodine or it may be directed specifically towards the iodoform molecule, in which case the patient's skin would react exclusively to iodoform and not to other compounds containing iodine. Another possible direction for the hypersensitivity is toward any methyl grouping in which one or more of the hydrogen atoms has been replaced by an iodine atom in which case the patient's skin would react also to methyl iodide.

In his brilliant discussion on the pathogenesis of eczema Bloch in 1924 reported on cross-sensitization in hypersensitivity to quinine, formalin and resorcinol. In a patient with eczematous hypersensitivity to quinine, patch tests were also positive to quinidine, cinchonine, cinchonidine, *optoquine, and quinoline* but were negative to pyridine. Bloch concluded that the cross-sensitization depended on the quinoline ring which was common to all the compounds producing positive reactions.

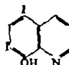
In a patient with allergic hypersensitivity to resorcinol he found a cross-sensitization among the dihydroxybenzenes (catechol, resorcinol, and hydroquinone) with the meta position of the hydroxyl groups being most allergenic.

In view of the fact that halogenated hydroxyquinolines are among the more commonly used topical therapeutic agents, cross-sensitizations produced by these compounds are of considerable practical interest. A representative study in three

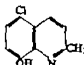
patients with cross-sensitization among halogenated hydroxyquinolines was carried out by Leifer and Steiner (1951). In one patient Diodoquin (5 7 diiodo-8-hydroxy quinoline) and in the other two persons Vioform (5 chloro-7 iodo-8 hydroxy quinoline) were the original sensitizing agents. It was found that all three patients reacted to the four most widely used compounds in this group, namely Vioform, Diodoquin, Quinolor and Sterosan, indicating beyond any doubt the existence of cross-sensitization. Only compounds which contained a hydroxyl-substituted quinoline elicited the reaction, while halogen substitution was not essential for the production of cutaneous reactions. Positive reactions were obtained also with carboxylated pyridines (picolinic acid and quinolinic acid) and these suggested that the halogenated hydroxy-quinolines are changed to carboxylated pyridines which are the actual antigenic complex. These studies elucidate the determining factor in at least some of the patients sensitive to halogenated hydroxyquinolines but they do not rule out other instances where different chemical units may determine the pattern of cross-sensitization.



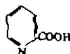
Vioform (5-chloro-7-iodo-8-hydroxy-quinoline)



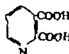
Diodoquin (5 7-diiodo-8-hydroxy quinoline)



Sterosan (5-chloro-8-hydroxyquinaldine)



α-Picolinic acid (2-pyridinecarboxylic acid)



Quinolinic acid (pyridine 2, 3-dicarboxylic acid)

Cross-sensitization among certain aromatic* amines

By far the best-studied example of cross-sensitization is one which encompasses a very large number of compounds and which at various times has been called either "cross-sensitization to compounds of quinone structure" (Mayer 1949) or sensitization to various substances containing a primary amino group in the para position (Flandin, Rabeau, Ukraincryk, 1936). The first and most basic work in this field was carried out by R. L. Mayer (1928) who was able to demonstrate in para-phenylenediamine hypersensitive patients a concomitant hypersensitivity to aniline (aminobenzene), methylaniline, aminophenol, diaminophenol, amino-azobenzene and various other amino-azo compounds as well as to a large series of chemically related substances.

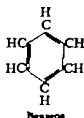
For footnote see next page.

All the substances which cross reacted in these patients shared the feature that they were capable of forming highly allergenic compounds of quinone structure in the course of their chemical transformation. Since the patients allergic hypersensitivity was usually directed towards these highly allergenic oxidation products and not towards the unaltered, less allergenic, para phenylenediamine, aminoazobenzene or para-aminophenol molecule, Mayer concluded that it is entirely reasonable that the skin should react to many or all substances which could form compounds of quinone structure in the skin.

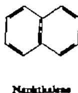
Much more recently Mayer (1950) summarized the present status of these theories and pointed out that among the compounds involved are some which are immunologically monovalent while others contain multiple immunologically active groups. In the case of the monovalent ones the allergic hypersensitivity may be limited to the sensitizing agent or it may extend to stereo-isomers, optical isomers and other *chemically related compounds. In the case of the multivalent allergens* it is only the activity exerted by the para aminobenzoic acid nucleus which is the important factor in the cross-sensitization under discussion here.

In Mayer's opinion, however the unaltered primary amino-group† cannot itself be the responsible factor in this sensitization because some compounds which

Aromatic compounds are cyclic structures containing conjugated double bonds as in benzene, naphthalene, or pyridine.

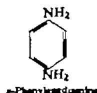


Benzene


Naphthalene



Pyridine



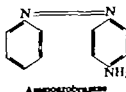
p-Phenylenediamine



Aniline



p-Aminophenol



Aminoazobenzene

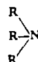
† A "primary" amine is a "derivative" of ammonia in which one hydrogen atom is replaced by an alkyl radical. In "secondary" amines two hydrogen atoms and in "tertiary" amines three hydrogen atoms are replaced by two and three alkyl radicals respectively



Primary amine



Secondary amine

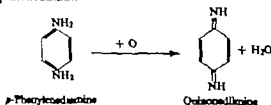


Tertiary amine

contain a primary amino-group do not cross-react. Further he states that a theory based on sensitivity to a primary amino-group could in no way explain cross-sensitizations involving certain nitro compounds such as picric acid. He explains the cross-sensitization as being due to common transformation products which result from (1) The oxidation of aromatic amines (2) the reduction of aromatic nitro compounds and (3) cleavage of the azo-linkage (–N=N–) leading to formation of two aromatic amines.

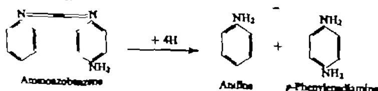
As discussed above, all these compounds in turn undergo oxidation and, depending upon their constitution, may be converted to quinoneimines, quinone diimines or their derivatives. These haptens may subsequently be reduced oxidized, polymerized, or conjugated. Their high allergenicity is due to their strong affinity for a variety of larger molecular substances, among them proteins and nucleoproteins.

According to Mayer the sequence of reactions leading to the formation of the active allergenic compounds is as follows. The skin oxidizes para-phenylenediamine to quinonediimine



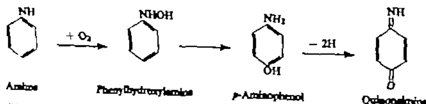
p-Phenylenediamine Quinonediimine

In the case of an azo dye such as aminoazobenzene this oxidation is preceded by a splitting of the azo compound into two amines by reduction of the azo-linkage leading, in this example, to the formation of aniline and paraphenylene diamine* The paraphenylenediamine is then oxidized to quinonediimine as shown above. This explains the cross-sensitization between paraphenylenediamine and aminoazobenzene.



Aminoazobenzene Aniline *p*-Phenylenediamine

According to Mayer aniline may then be transformed into quinoneimine as follows



Aniline Phenylhydroxylamine *p*-Aminophenol Quinoneimine

* Obviously the constitution of the amines which result from this cleavage depends on the constitution of the original azo compound.

He described, however cases of hypersensitivity to paraphenylenediamine alone or to aminoazobenzene alone without the occurrence of cross reactions which are similar to patients reported by Sidi (1945) with a specific allergic sensitivity to paraphenylenediamine and/or paratoluylenediamine which did not extend to substances which theoretically would be expected to form compounds of quinone structure Mayer postulates that in such patients there might have been a disturbance in the oxidation or reduction processes in the skin which would have prevented the formation of compounds of quinone structure or the hypersensitivity might have been specifically directed towards only one quinone compound without having extended to all other quinone compounds. Attention was called, even at that relatively early date, to the great practical significance of these cross-sensitizations, because of the widespread use of substances in the fur dyeing industry and in cosmetics, leather clothing materials and topical therapeutic agents (scarlet red, pellidol) which could form compounds of quinone structure.

Nitti, Bovet and Depierre (1937) commented upon the optimal steric configuration leading to allergenic activity They expressed the opinion that the sensitizing capacity of paraphenylenediamine is due to two factors (*a*) The molecular structure, the para* position being eminently favourable for the production of allergic phenomena and (*b*) the lability and reactivity of the amino group in the molecule.

In justice to those authors who have not agreed with Mayer's theories, it must be admitted that at the present time there is no reliable evidence to explain how such common transformation products are formed from some of the very important compounds which participate in the cross sensitization such as para-aminobenzoic acid and the sulphonamides.

A patient with an exceedingly wide sensitization spectrum studied by Meltzer and Baer (1949) had had atopic dermatitis and seborrhoeic dermatitis since the age of 18 years. While these eruptions were quiescent he developed occasional bouts of acute dermatitis on the face, hands and feet. It was found subsequently that the following allergic sensitivities accounted for at least some of these episodes (1) Sensitivity to benzocaine discovered by patch test in 1939 (2) sensitivity to a sulphonamide, probably sulphaguanidine, noted clinically in 1944 and (3) sensitivity to a sunburn preventive containing monoglycerol para-aminobenzoate, noted clinically in 1947 The close chemical relationship of these compounds was so obvious as to suggest patch tests with a great number of other chemically related substances. Table I lists the results of these skin tests carried out in 1948

* "Para" position denotes replacement of the H atoms in the 1 4 positions on the benzene ring.
"Meta" position denotes replacement of H atoms in the 1 3 positions.
"Ortho" position denotes replacement of H atoms in the 1 2 positions.

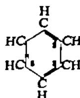


TABLE I

RESULTS OF PATCH TESTS ON R. R.

Substance	*Chemical structure*	*Reaction*
Benzocaine	H_2N–⬡–$C(=O)–OC_2H_5$	+ + + +
Butesin	H_2N–⬡–$C(=O)–OC_4H_9$	+ + + +
Para-aminobenzoic acid	H_2N–⬡–$C(=O)–OH$	+ + + +
Para-phenylenediamine	H_2N–⬡–NH	+ + + +
Aniline	H_2N–⬡	+ + + +
Monoglycerol para-amino-benzoate	H_2N–⬡–$C(=O)–CH_2CHOHCH_2OH$	+ + + +
Procaine	H_2N–⬡–$C(=O)–O–C_2H_4N(C_2H_5)_2$	+ + + +
Sulphaguanidine	H_2N–⬡–$S(=O)(=O)–N=C(NH_2)(NH_2)$	+ + +
Sulphanilamide	H_2N–⬡–$S(=O)(=O)–NH_2$	+ + +
Saccharin	⬡ fused ring with C, NH, S(O)(O)	+ +

He described, however cases of hypersensitivity to paraphenylenediamine alone or to aminoazobenzene alone without *the occurrence of cross-reactions* which are similar to patients reported by Sidi (1945) with a specific allergic sensitivity to paraphenylenediamine and/or paratoluylenediamine which did not extend to substances which theoretically would be expected to form compounds of quinone structure. Mayer postulates that in such patients there might have been a disturbance in the oxidation or reduction processes in the skin which would have prevented the formation of compounds of quinone structure or the hypersensitivity might have been specifically directed towards only one quinone compound without having extended to all other quinone compounds. Attention was called, even at that relatively early date, to the great practical significance of these cross-sensitizations, because of the widespread use of substances in the fur dyeing industry and in cosmetics, leather clothing materials and topical therapeutic agents (scarlet red, pellidol) which could form compounds of quinone structure.

Nitti, Bovet and Depierre (1937) commented upon the optimal steric configuration leading to allergenic activity They expressed the opinion that the sensitizing capacity of paraphenylenediamine is due to two factors (*a*) The molecular structure, the para* position being eminently favourable for the production of allergic phenomena, and (*b*) the lability and reactivity of the amino group in the molecule.

In justice to those authors who have not agreed with Mayer s theories, it must be admitted that at the present time there is no reliable evidence to explain how such common transformation products are formed from some of the very important compounds which participate in the cross-sensitization such as para-aminobenzoic acid and the sulphonamides.

A patient with an exceedingly wide sensitization spectrum studied by Meltzer and Baer (1949) had had atopic dermatitis and seborrhoeic dermatitis since the age of 18 years While these eruptions were quiescent he developed occasional bouts of acute dermatitis on the face, hands and feet. It was found subsequently that the following allergic sensitivities accounted for at least some of these episodes (1) Sensitivity to benzocaine discovered by patch test in 1939 (2) sensitivity to a sulphonamide, probably sulphaguanidine, noted clinically in 1944 and (3) sensitivity to *a sunburn preventive containing monoglycerol* para-aminobenzoate, noted clinically in 1947 The close chemical relationship of these compounds was so obvious as to suggest patch tests with a great number of other chemically related substances. Table I lists the results of these skin tests carried out in 1948

* "Para" position denotes replacement of the H atoms in the 1 4 positions on the benzene ring.
"Meta" position denotes replacement of H atoms in the 1 3 positions.
"Ortho" position denotes replacement of H atoms in the 1 2 positions.

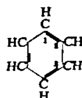


TABLE I (*continued*)

Substance	*Chemical structure*	*Reaction*
Apothesine	$HC{=}CH\ \overset{O}{\overset{\Vert}{C}}{-}O{-}C_3H_6N(C_2H_5)(C_2H_5)$	0
Methyl anthranilate	NH_2, $COOCH_3$	0
Pontocaine	C_4H_9, HN, $\overset{O}{\overset{\Vert}{C}}{-}OC_2H_4N(CH_3)(CH_3)$	0
Phenol	OH	0
Anthranilic acid	NH_2, $COOH$	0
3, 5 Dinitrobenzoic acid	O_2N, NO_2, $\overset{O}{\overset{\Vert}{C}}{-}OH$	0
Paranitrobenzoic acid	NO_2, $\overset{O}{\overset{\Vert}{C}}{-}OH$	0

Table II presents a comparison between the cross-reactions elicited in patch tests in an unselected group of 7 very strongly paraphenylenediamine sensitive subjects (4 + patch test reaction) with the reactions in 7 unselected subjects with relatively weak reactions (2 + patch test reaction) to paraphenylenediamine. The results of these tests demonstrate that, as has been stressed previously by other authors, the stronger the hypersensitivity to the primary allergen the greater the tendency to cross-sensitization.

TABLE I (*continued*)

Substance	*Chemical structure*	*Reaction*
Azodye "A"	CH_3CONH–(ring)–N=N–(ring with Cl, OH)	+ +
Picric acid	(ring with OH, O_2N, NO_2, NO_2)	+ + +
Sulphadiazine	H_2N–(ring)–S(=O)(=O)–N(H)–C (ring N–CH, CH, N–CH)	+
Nupercaine	(quinoline ring, N) with $CONHC_2H_4N(C_2H_5)_2$ and –O–C_4H_9	+
Azodye "B"	O_2N–(ring)–N=N–(ring)–N(C_2H_5)(C_2H_4OH)	0
Stovaine	(ring)–C(=O)–O–C(CH_3)(C_2H_5)–$CH_2N(CH_3)_2$	0
Alypin	(ring)–C(=O)–O–C(C_2H_5)(CH_2–CH_3NCH_3)–$CH_2N(CH_3)_2$	0

The great practical significance of this observation lies in the probability that oft-repeated exposure to the primary allergen is not only likely to increase, rather than decrease, the degree of sensitivity to the primary allergen itself, but that it also will tend to widen the pattern of cross-sensitization.

This relatively specific widening of the pattern of sensitization must not be confused with the so-called non-specific polyvalent sensitivity which has been described as occurring in patients with severe dermatitis when the patient, more or less suddenly reacts to many chemically *unrelated* substances. Since it is probably based on irritability of the skin rather than on specific immunological mechanisms, polyvalent non-specific sensitivity usually disappears soon after the acute severe dermatitis has subsided. On the other hand, in specific cross-sensitization our experience suggests that the added sensitivities usually persist for an indefinite period of time

Cross-sensitization among local anaesthetics and certain aromatic amines

Cross-sensitization among paraphenylenediamine and certain local anaesthetics (such as Orthoform, benzocaine, procaine, Scuroform, Stovaine) was reported by Flandin, Rabeau and Ukrainczyk (1936), Tzanck (1942), Sidi (1945) and many others. It was well illustrated by a patient of Tzanck (1942) who first had a widespread dermatitis due to the topical application of picric acid for shingles then another widespread eruption due to the application of a local anaesthetic ointment for haemorrhoids then a dermatitis of the upper lip after dyeing his moustache with a dye which probably contained paraphenylenediamine then a dermatitis of the face after receiving local anaesthesia from his *dentist* and finally a scrotal dermatitis after the use of an ointment containing cocaine. Another patient cited by Tzanck was an operator in a hairdressing establishment who had had a dermatitis of the hands from paraphenylenediamine and then developed a severe flare-up of this dermatitis after her dentist had injected her gums with a local anaesthetic.

Flandin, Rabeau and Ukrainczyk (1936) reported the intriguing observation that patients with primary sensitization to aniline and cross-sensitization to local anaesthetics appeared to have a greater degree of sensitivity to aniline than to the local anaesthetics however patients with primary sensitization to one of the local anaesthetics and cross-sensitization to aniline appeared to have a greater degree of sensitivity to aniline than to the local anaesthetic, despite the fact that aniline was only a secondary allergen to which they presumably had never been exposed. A perfect parallel to this important observation is found in studies of Sidi (1945) who called attention to the fact that while the large majority of his patients with primary sensitization to local anaesthetics had developed cross-sensitization to paraphenylenediamine, only a minority of those with primary sensitization to paraphenylenediamine manifested cross-sensitization to local anaesthetics. Subsequently Tzanck, Sidi and Dobkevitch-Morrill (1950) reported that (*a*) Subjects

The phenomenon where immuno-chemically *unrelated* substances produce flare-ups in healed sites of allergic eruptions or skin test reactions requires further study. Some or all such flare-ups may be based on non-specific mechanisms. In reactions to the more complex allergens the possibility of group reactions cannot be completely excluded because usually not all constituents of the allergens in question are known.

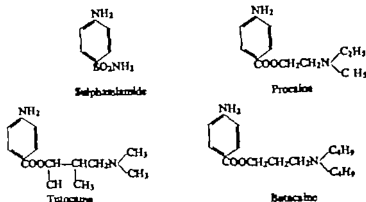
TABLE II

COMPARISON OF CROSS-SENSITIZATION PATTERN IN 7 SUBJECTS WITH STRONG HYPERSENSITIVITY AND 7 WITH WEAK HYPERSENSITIVITY TO *p*-PHENYLENEDIAMINE

		p-Phenylene-diamine	*Aniline*	*FDC & C Yellow #6†*	*Acetamine Yellow*	*Acetamine Scarlet*	*Nylon Hose*	*p-Aminobenzoic Acid*	*Anthranilic Acid (o-Aminobenzoic Acid)*	*m-Aminobenzoic Acid*	*3 5 Dinitrobenzoic Acid*	*p-Nitrobenzoic Acid*	*Pontocaine*	*Procaine*	*Benzocaine*	*Sulphanilamide*	*Sulphadiazine*	*Procaine Penicillin*	*Picric Acid*
Subjects with strong patch test reactions to *p*-phenylenediamine	1	4+	1+	1+	1+	2+	0	2+	1+	0	0	0	0	0	0	0	0	0	0
	2	4+	3+	3+	3+	0	2+	3+	2+	0	0	0	0	0	0	0	0	0	0
	3	4+	2+	2+	0	2+	1+	3+	1+	0	0	0	0	3+	3+	0	0	4+	0
	4	4+	3+	0	1+	1+	0	1+	2+	0	0	0	0	1+	2+	0	0	0	0
	5	4+	0	3+	3+	3+	3+	0	0	0	0	2+	0	0	0	0	0	0	0
	6	4+	0	0	2+	2+	3+	1+	0	0	0	0	1+	1+	1+	0	1+	1+	0
	7	4+	4+	3+	4+	4+	3+	0	0	0	0	0	0	0	0	0	0	0	0
Subjects with relatively weak patch test reactions to *p*-phenylene-diamine	1	2+	0	0	0	2+	0	1+	0	0	0	0	0	0	2+	0	0	0	0
	2	2+	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	3	2+	0	0	0	1+	0	0	0	2+	0	0	2+	0	2+	0	0	0	0
	4	2+	0	0	1+	0	0	0	0	0	0	0	0	0	2+	0	0	1+	0
	5	2+	0	0	1+	1+	0	0	0	0	0	0	0	0	2+	0	0	0	0
	6	2+	0	0	0	1+	0	3+	0	0	0	0	0	0	1+	3+	0	0	0
	7	2+	0	0	0	2+	1+	2+	0	0	0	0	0	0	0	0	0	0	0

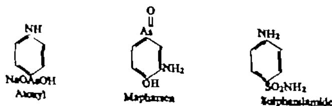
Azodye used for colouring stockings.
† Azodye used for colouring foods and beverages.

Clinical evidence of the cross-sensitization between sulphonamides and local anaesthetics was reported by Rogers as early as 1938. He gave an account of a patient who after taking sulphanilamide, developed a dermatitis in all those skin areas which years before had at various times been the sites of an allergic dermatitis due to procaine, tutocaine and butacaine.



The realization that in many patients the aminophenyl grouping is the determining factor in allergic sensitization engendered by sulphonamides made it exigent to investigate the other aromatic amines which participate in the cross-sensitization. As was to be expected, cross-sensitizations were discovered to many related compounds, among these being paraphenylenediamine and local anaesthetics (Tzanck, Sidi and Roujeau, 1947) and para-aminobenzoic acid (Sulzberger Kanof, Baer and Lowenberg, 1947). Kooij and van Vloten (1952) and Rajka (1952) demonstrated again that sulphonamide sensitivity extended to a wide variety of substances containing the para-aminophenyl radical by testing a considerable number of patients who had recovered from sulphonamide eruptions with many chemically related compounds.

In a few of their sulphonamide-sensitive patients Kooij and van Vloten elicited reactions also to atoxyl, Mapharsen and neoarsphenamine. They point out, however that another group of patients who had recovered from a dermatitis due to neoarsphenamine did *not* yield patch test reactions to sulphonamides or other compounds containing aromatic amines. The reason for the lack of cross-sensitization to sulphonamides in the patients with primary sensitization to these organic arsenicals is that the sensitization extended only to related compounds which contain arsenic in the molecule rather than to compounds containing the aminophenyl grouping. Therefore, aromatic amines containing no arsenic will not cross-react.



with primary sensitization to sulphonamides cross react to paraphenylenediamine and to synthetic local anaesthetics in 100 per cent of cases (*b*) subjects with primary sensitization to local anaesthetics cross react to paraphenylenediamine in 90 per cent of cases and (*c*) subjects with primary sensitization to paraphenylenediamine cross-react to local anaesthetics only in slightly less than 20 per cent of cases. An example of the identical phenomenon in cross-sensitization among larger molecular compounds is cited by Fisher (1952). He observed that of 18 patients with allergic eczematous sensitivity to the oleoresin of ragweed all reacted to the oleoresin of pyrethrum whereas only 3 out of 8 pyrethrum-sensitive subjects reacted also to ragweed oleoresin

In primary allergic eczematous sensitization we are accustomed to refer to the sensitizing index of an allergen, indicating that each allergen under standard conditions, has a rather consistent capacity to sensitize the skin of a certain percentage of those exposed. The examples cited above show that the same does not always hold true in cross sensitization, where the capacity of any one substance to become a *secondary* allergen may depend on the chemical constitution of the *primary* allergen

In a separate section more will be said about cross-sensitization among the different groups of local anaesthetics, much of it without direct bearing on sensitization to compounds of quinone structure.

Cross-sensitization among sulphonamides and other aromatic compounds

The relatively common occurrence of allergic eruptions due to oral and topical administration of sulphonamides which was noted early during the sulphonamide era presented an unequalled opportunity for the study of cross-sensitization among these drugs. Some reports described patients who developed eczematous and other forms of allergic sensitizations (Peterkin, 1945) which were highly specific for only one sulphonamide. No evidence of cross-sensitization even to closely related compounds was brought to light.

In many patients, however the sensitization extended to several or all other sulphonamides tested At that time the modern antibiotics were not yet available and the absolute specificity or the lack of specificity of the sulphonamide sensitization was of much practical importance. Whenever cross-sensitization extended to all other available sulphonamides there was the possibility that the patient might not be able to receive specific chemotherapy for some of the most important and potentially serious infections. Park (1944) showed that in many of the patients sensitive to sulphonamides the sensitization extended to procaine and sulphanilic acid as well as to other sulphonamides, indicating that the sensitivity was directed towards the para-aminophenyl radical rather than towards the para-aminophenyl sulphonic acid radical.

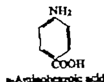


p-Aminophenyl radical



p-Aminophenylsulphonic acid radical

benzoic acid is now prescribed for systemic use as a chemotherapeutic agent and as a vitamin factor

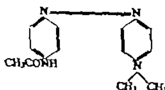


p-Aminobenzoic acid

Strong cross-sensitization to para-aminobenzoic acid in a procaine allergic patient was reported by M. H. Goodman (1939) and cross-sensitization in three out of eight subjects sensitive to sulphonamides was observed by Sulzberger, Kanof, Baer and Lowenberg (1947). Another excellent example of this cross-sensitization is the patient whose sensitivity pattern is shown in Table I. On two occasions he developed a severe contact dermatitis due to the para-aminobenzoic acid ester in a sunburn preventive and his patch test reaction to para-aminobenzoic acid was among the strongest elicited on his skin. Tzanck and Sidi (1950), Rajka (1952), and our own group have seen a number of paraphenylenediamine sensitive subjects with positive patch tests to para-aminobenzoic acid. Our experience, however, supports the opinion of Tzanck and Sidi that eruptions due to para-aminobenzoic acid are not common clinically.

Cross-sensitization among azodyes and certain aromatic amines

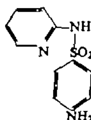
The cross-sensitization involving azodyes is of special interest at the present time for two principal reasons. The extensive use of azodyes for many different purposes leads to virtually uninterrupted exposures of hundreds of millions of people by contact and by ingestion. Among these is the use of azodyes in clothing, leather, drugs, cosmetics, stockings, gasoline and the colouring of foods and beverages. Further, many azodyes possess a low sensitizing capacity and therefore cutaneous eruptions produced by them are usually due to their activity as secondary allergens. This holds true especially for azodyes used for colouring foods. The primary sensitization in such cases is engendered by related compounds which have a greater sensitizing capacity such as benzocaine, sulphonamides, paraphenylenediamine, etc. As a matter of fact the sensitizing capacity of certain azodyes is so low that Mayer likes to speak of many of them as elicitors. An absolute differentiation, however, between elicitors and sensitizers cannot be made here because in exceptional instances these same azodyes have been shown to be capable of engendering allergic sensitization (Fisher, 1952).



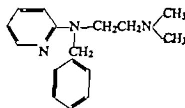
Example of an azodye used in colouring nylon stockings

At the present time azodyes are used for colouring foods in many civilized countries. In the United States, for example, 10 out of the 18 dyes which are accepted by the government for use in foods are azodyes. The colouring of

It would be wrong to assume that allergic sensitization to a sulphonamide must always be specifically directed either towards the whole sulphonamide molecule or towards the para-aminophenyl radical or the para aminophenylsulphonic acid radical. In exceptional cases the allergenic activity appears to be dependent upon the radical which is attached to the SO_2 grouping. In that event other varieties of cross-sensitizations may be seen. An interesting example is the cross-sensitization between sulphapyridine and pyribenzamine in patients who have developed an allergic sensitization to the pyridine ring contained in both compounds (Peck 1950).



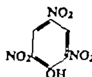
Sulphapyridine



Pyribenzamine

Cross-sensitization among certain aromatic nitro compounds and aromatic amines

Lipschütz (1920) is credited with having been the first to suggest that human tissues have the capacity to reduce nitro groups to amino groups. Many clinical observations support the occurrence of this biochemical transformation in the human skin although there is no exact knowledge as to the chemical steps involved The previously cited case of R Tzanck (1942) with a primary sensitization to picric acid (trinitrophenol) and secondary sensitization to local anaesthetics and para phenylenediamine is an example of this cross-sensitization



Picric acid (Trinitrophenol)

Sidi (1945) observed several patients with a cross-sensitization between picric acid or paranitrophenol and paraphenylenediamine. In our own unpublished studies we found that among 53 paraphenylenediamine-sensitive subjects there were only three with a cross sensitization to picric acid These results and those in other smaller series of tests (for example, Rajka, 1952) indicate that cross sensitization to picric acid occurs only in a small percentage of patients with allergic sensitivity to aromatic amines

Cross-sensitization between para-aminobenzoic acid and certain aromatic amines

This form of cross-sensitization has not been studied by many investigators, probably because para aminobenzoic acid was not used on the skin or as a systemic therapeutic agent until a few years ago At the present time para-aminobenzoic acid and its esters are, at least in the United States, among the most commonly used chemical filters in commercial sunburn preventives. Moreover para-amino-

titis was made to recur or to flare-up by the ingestion and injection of the allergenic aromatic amine. In eleven out of twenty-five cases existence of cross-sensitization was conclusively demonstrated by deliberately causing recurrence or exacerbation of eruptions through ingestion or injection of *secondary* allergens. Aggravation of the eruption with itching and sometimes even systemic reactions (syncope, chills, delirium, fever) were caused by ingestion or injection of procaine in sulphonamide-sensitive patients, of sulphonamides in local anaesthetic-sensitive patients, and of sulphonamides in paraphenylenediamine-sensitive patients.

Cross-sensitization among local anaesthetics

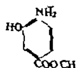
In our own experience local anaesthetics, as a group, cause a higher incidence of allergic contact dermatitis than any other group of compounds used in dermatological therapy at the present time. This impression is supported by the fact that the pharmaceutical industry frequently places new local anaesthetics on the market, often with the claim of having found a compound which is either non-sensitizing or which has a significantly lower sensitizing capacity than the previously available local anaesthetics.

Most clinicians have had the experience that patients who have shown evidence of allergic eczematous sensitization to one local anaesthetic compound are likely to show allergic reactions to some of the other local anaesthetics as well. Careful studies over a period of many years have demonstrated that such multiple sensitizations to local anaesthetics do not occur in a haphazard fashion. In many of the cases which have been investigated one has been able to show that reactions to several local anaesthetics in the same patient are due to cross-sensitizations which are patterned on the basis of one or more particular chemical features which are responsible for the specificity of the allergic sensitization. Yet it is undeniable that in some cases of sensitization to several local anaesthetics no consistent immunochemical pattern can be demonstrated (Sulzberger and Wise, 1933 Strauss, 1947)

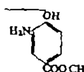
The work done to date indicates that one or more of the following chemical groupings may determine the pattern of cross-reactions among local anaesthetics

(*a*) An OH group in the para- or meta-position on para-aminobenzoic acid (Schwarzschild, 1928).

It as shown that in sensitization to Orthoform (*p*-amino-*m*-hydroxybenzoic acid methyl ester) the presence of the —OH group in the para or meta position of the aminobenzoic acid radical was the determining factor Patients sensitive to Orthoform reacted also to Neo-Orthoform (*m*-amino-*p*-hydroxybenzoic acid methyl ester) but in general did *not* react to the alkyl esters of *p*-aminobenzoic acid.



Orthoform† (*p*-amino-*m*-hydroxybenzoic acid methyl ester)



Neo-Orthoform (*m*-amino-*p*-hydroxybenzoic acid methyl ester)

(*b*) A tertiary amine in the ester side chain (James, 1931).

Alkyl group is one with the same general formula C_nH_{2n+1}.
† The dotted line indicates that part of the molecule which is significant in the particular cross-sensitization

prepared foods and beverages, especially soft drinks, is so common that the average American rarely spends a day when he is not exposed to traces of these dyes It was, therefore, necessary to ascertain whether these particular azodyes participate in the cross-sensitization in subjects sensitive to certain aromatic amines Patch test reactions with these dyes in a series of patients who were strongly hypersensitive to paraphenylenediamine *were so much stronger than in* non-sensitive control cases that it becomes likely that hypersensitivity to aromatic amines extends to certain azodyes found in many foods (Baer Leider Mayer *1948)* The question then arises whether the patch-test sensitivity to these food azodyes is also accompanied by clinical sensitivity In seven out of twenty subjects hypersensitive to paraphenylenediamine, the feeding of food azodyes (without adding them first to foods) appeared to produce increased itching and exacerbations of the skin lesions, and in five additional subjects only an increase in itching was *noted (Baer and Leider 1949) The azodyes which appeared to cause "flare ups"* were those listed by the United States Food and Drug Administration as FD&C Orange #2 (1-ortho-tolylazo 2 naphthol), FD&C Yellow #3 (1 phenylazo ? naphthylamine) and FD&C Yellow #6 (disodium salt of 1 p-sulphophenylazo 2 naphthol -6-sulphonic acid). Rajka (1952) confirmed these results in a few of his patients in whom the deliberate feeding of the azodyes acid yellow (mixture of sodium 4-aminoazobenzene mono- and di-sulphonate) and amaranth (sodium 2-oxy 1 1 azonaphthalene 3 7 4 trisulphonate) caused flaring up of the eruption and itching.

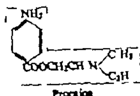
Since these data were published the present author has had a number of personal communications concerning patients in whom the clinical evidence strongly suggested that the ingestion of foods or drugs coloured with certified food azodyes caused symptoms on skin areas which at some previous time had been the sites of dermatitis due to certain related aromatic amines In no instance, however was an attempt made to prove the role of the food azodyes by deliberately feeding them to these patients

When considering the possible clinical significance of these findings one must appreciate that the quantities of food azodyes which were administered in the deliberate feeding experiments were presumably much greater than would be encountered in non-experimental exposures Further there were a number of complicating experimental conditions which alone would preclude definite conclusions Nevertheless it may be inferred that there is now a definite possibility that these supposedly entirely innocuous and non-sensitizing food azodyes might produce increased itching and might in general contribute to the maintenance and *prolongation of eruptions caused" by chemically related aromatic amines* with a greater sensitizing capacity

Over a period of more than five decades much incontrovertible evidence has been accumulated which demonstrates that the ingestion inhalation or *injection of* eczematogenic allergens may in exceptional cases *cause* allergic eczematous sensitization and may if the quantity of allergen is sufficiently large *elicit* eczematous responses in skin which has been previously sensitized, usually by the epicutaneous route. Therefore, it should not come as a great surprise that allergenic aromatic *amines and their transformation* products can also elicit clinical signs and symptoms when administered by these more unusual routes. Sidi and Doblevitch-Morrill (1951) cited a whole series of patients in whom allergic eczematous derma

CROSS-SENSITIZATION AMONG ECZEMATOGENIC ALLERGENS

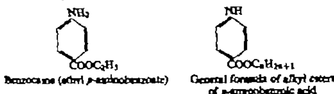
Absence of the aromatic amino group abolished the capacity to produce reactions but substitution of H atoms by alkyl groups in the side chain or of one H atom in the aromatic amino group did not abolish it.



Procaine

(*f*) An alkyl ester of para-aminobenzoic acid (Laden and Rubin, 1947).

In a patient with a contact dermatitis due to Butesin Picrate ointment it was shown that the sensitivity extended to *all* homologous alkyl esters of para-aminobenzoic acid. The sensitivity increased with lengthening of the side chain from the methyl to the ethyl to the propyl ester and decreased with further lengthening of the side chain to the butyl and amyl esters. It is interesting to note that, although this patient had undergone primary sensitization to the butyl ester of para-aminobenzoic acid, his cross-sensitization to the propyl ester was found to be one hundred times stronger!



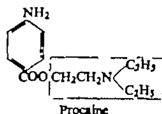
Benzocaine (ethyl *p*-aminobenzoate)   General formula of alkyl esters of *p*-aminobenzoic acid

The width of the cross-sensitization pattern in allergic sensitivity to local anaesthetics depends obviously on the particular group or groups towards which the primary sensitization is *directed* and on the additional sensitizations to other chemical complexes which have developed subsequent to the primary sensitization. If the sensitization, for example, is to some or *all* compounds of quinone structure then only those local anaesthetics which in the skin can be transformed into quinone compounds will be involved. If the sensitization is to compounds which contain a primary amino group in the para position on the benzene ring then only substances which contain this particular chemical complex can cross-react. The sensitivity pattern of the patient shown in Table I appears to bear this out quite well: there were strong reactions to benzocaine and procaine, a very weak reaction to Nupercaine and no reaction to Stovaine, alypin, Apothesine or Pontocaine. The latter group of local anaesthetics either have no amino group in the para position or possess decreased allergenicity because of substitution of the amino group (Mayer 1928).

CROSS-SENSITIZATION AMONG URTICARIOGENIC ALLERGENS

There are relatively few reports in the literature dealing with systematic studies on urticarial cross-sensitizations among simple chemicals in human beings. This is not surprising because many cases of allergic urticaria are caused by large molecular substances (for example, protein allergens in foods, inhalants, parasites) rather than by simple chemicals. Further in most patients with urticaria, skin testing with the causal agent fails to elicit an immediate wheal response, a fact which makes it almost impossible to carry out detailed studies from the standpoint of cross-sensitization.

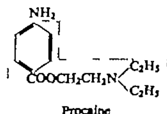
It was shown in a case of procaine dermatitis that the sensitivity was directed against *aliphatic tertiary amines* because there was a reaction to the diethylaminoethyl side chain alone without the ring part of the procaine molecule.



Procaine

(c) Benzoic acid esters containing tertiary amines in the side chain (Waldron, 1934).

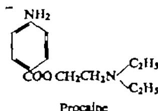
It was shown that a dentist reacted to a number of local anaesthetics all of which *contained a benzoic acid radical esterified with a residue containing a tertiary amine.* While the tests were not sufficiently extensive to permit definite conclusions, the amino group in the para position on the benzene ring was apparently without significance *for the allergic sensitization*



Procaine

(d) *Para-aminobenzoyl group (M H Goodman, 1939)*

It was shown that the sensitivity of the patient, who had become allergic to procaine in an eyewash, extended to all those compounds, local anaesthetic or otherwise, which *contained the para-aminobenzoyl group* and that substitution in the ester side chain attached to the carboxyl group did not appear to play a decisive role

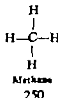


Procaine

(e) A secondary or tertiary amine in the ester group of the para-aminobenzoic acid ester (Rothman, Orland and Flesch, 1945)

It was shown that the procaine sensitivity of the dentist extended to a whole group of local anaesthetics which were esters of para-aminobenzoic acid containing a secondary or tertiary amine in the ester side chain, the length of the side chain being irrelevant

Aliphatic compounds are open-chain compounds derived from *paraffin hydrocarbons* such as methane, ethane, etc.



Methane

become customary to ascertain the sensitizing capacity of newly-developed materials for consumer use by means of a bio-assay This is usually carried out first in experimental animals and then in about 100 to 300 human volunteers who receive one or more patch-test exposures to the material under investigation. After allowing an appropriate time for the development of allergic sensitization (usually three or more weeks), they undergo another exposure in order to reveal how many in the group have become sensitized to the material.

Many dermatologists have been aware of the obvious shortcomings of this form of bio-assay which is incapable of duplicating actual clinical conditions and which furnishes results of very limited value statistically (Henderson and Riley 1945). Nevertheless, the method is widely used because of its merits as a preliminary screening procedure. The value of such bio-assays is further impaired by the fact that they are adequate only for the detection of *sensitizing* agents. Those substances which commonly or invariably act as *elicitors* will of necessity escape detection although under actual clinical conditions they may cause severe allergic reactions.

New procedures could be devised which may provide information regarding the probability of reactions of cross-sensitization due to new materials which, in the conventional bio-assay have shown themselves devoid of allergic sensitizing properties. A group of volunteers, known to be strongly hypersensitive to chemically related agents known to possess a *high* sensitizing potential, can be patch tested with the non-sensitizing material under study Negative results of such tests cannot assure that the new material will not elicit allergic reactions on the basis of cross-sensitization in *some* persons, but they will indicate that a *high* incidence of allergic reactions is unlikely to occur

Other possible applications of the concept of cross-sensitization

The data presented here prove that the phenomenon of cross-sensitization plays a significant role in the course of allergic eruptions in some patients. Does this phenomenon occur also in allergic diseases affecting other organs or structures? We know that cross-sensitization among the allergenic protein and oleoresin fractions of certain pollens, other inhalants and foods are of much practical importance. They often allow the physician to use one representative allergen rather than a mixture of allergens in the skin testing and treatment of patients with certain allergic diseases, especially those affecting the respiratory organs and the gastro-intestinal tract. Apart from the allergic diseases mentioned above almost no work has been done on cross-sensitization. Among the weightiest reasons for the lack of pertinent investigations in this field is the previously stated inherent difficulty in studying those cross-sensitizations which are not accompanied by positive skin reactions to the participating allergens.

For many years there have been indications that some cases of thrombocytopenic purpura are based on an allergic mechanism, because the purpuric and other manifestations recurred repeatedly upon the re-administration of small or even minute quantities of the causal food or drug. *It is, therefore* not surprising that a few such cases have been investigated for the possible existence of cross-sensitization.

For example in a case of thrombocytopenic purpura due to sulphathiazole Hurd and Jacox (1943) were able deliberately to induce recurrences through the oral administration of either sulphathiazole or sulphadiazine. The manifestations of

The first systematic study on urticarial cross-sensitization among simple chemical compounds which has come to our attention was carried out by Dawson and Garbade (1930) in a patient with urticaria due to quinine and cinchonidine. Urticarial skin reactions were elicited not only to quinine and cinchonidine but also to the related laevorotatory alkaloids hydroquinine, hydrocinchonidine, cupreine, hydrocupreine, ethylhydrocupreine and ethylquitenine. No reactions were produced by the dextrorotatory isomers nor by certain closely related laevorotatory alkaloids, for example, nitro-hydroquinine, iso-amyl-hydrocupreine and iso-octyl-hydrocupreine.

Most interesting is the case of a laboratory worker whose chronic urticaria was traced to exposure to formaldehyde, tobacco smoke (both from the patient's own smoking and that of others in his environment) and certain fried and broiled foods (Rappaport and Hoffman, 1941). Investigation showed that the cross-sensitization extended to aliphatic non-conjugated aldehydes ranging from formaldehyde to an eighteen chain aldehyde. The reaction-producing concentration ranged from 1 : 1 000 000 for formaldehyde to 1 : 1 for the aldehyde containing eighteen carbon atoms, indicating that the shorter the carbon chain the more marked was the reaction. Aliphatic conjugated and aromatic aldehydes failed to produce urticarial skin reactions with the exception of acrolein.

Urticarial sensitization "fixed" to one skin site and accompanied by anaphylactoid symptoms has been reported (Sievers, Morey and Samter, 1949) due to bromsulphalein (disodium tetrabromophenolphthaleinsulphonate). The tetrachloro-analogue of this compound elicited an equally strong reaction, but reactions could not be produced with the halogen-free analogue (sodium phenolphthalein sulphonate) nor with two compounds representing parts of the bromsulphalein molecule, namely phenolsulphonic acid and disodium tetrabromophthalate. These results did not permit any definite conclusions as to the exact part of the bromsulphalein molecule responsible for the urticarial sensitization.

SOME PRACTICAL APPLICATIONS OF CROSS-SENSITIZATION

Several important considerations make cross-sensitizations a phenomenon of great clinical significance to the dermatologist. Formerly, for instance, it was difficult or impossible for the clinician to understand why he sometimes saw patients who had developed an allergic eruption after exposure to one or more compounds to which they have never previously been exposed. This was in contradiction to the accepted definition of allergic sensitization which requires adequate previous exposure to a given compound before such sensitization can occur. The concept of cross-sensitization, however, easily explains how a *first* exposure to secondary allergens may engender an allergic eruption.

Another hitherto largely unexplained occurrence is the persistence of allergic eruptions in some patients for weeks, months, and even years, despite the most careful avoidance of the causal agent or agents. It appears entirely possible, even likely, that many patients whose allergic eruption persists in such a way may undergo more or less frequent occult exposures to compounds which are immunochemically related to the primary allergen. It is these secondary allergens which in all probability account for the persistence of the initial eruption.

In the future it may be advisable to give more consideration to cross-sensitization in connexion with problems of preventive dermatology. In many places it has

sensitizations is agranulocytosis due to drugs (Squier and Madison, 1934 Kracke and Parker 1934). What happens to the blood counts of patients who have had agranulocytosis due to allergic sensitization to one sulphonamide, when they are subsequently exposed to another sulphonamide or to other aromatic amines such as procaine injections given by the dentist, ingestion of food coloured with azodyes, etc.? Do they manifest a drop in the number of leucocytes under such circumstances and, if so, how long will the granulocytopenic reaction last? In this connexion it is pertinent to recall the report of Squier and Madison (1934) of two patients who had recovered from agranulocytosis due to amidopyrine and/or Allonal. Twenty-four hours after application of patch tests with amidopyrine and Allonal there were eczematous skin reactions to both drugs as well as clinical and haematologic evidence of agranulocytosis! These findings to some extent are supported by the observations of Dameshek (1936) of patients who had recovered from agranulocytosis due to amidopyrine. Complete clinical and haematologic evidence of agranulocytosis was noted shortly after an intracutaneous test with a minute quantity of amidopyrine.

One can speculate further about the role of cross-sensitizations in diseases affecting organs other than the skin. These examples should suffice to suggest possible avenues for future investigations dealing with the application of the concept of cross-sensitization in medicine in general

CROSS-SENSITIZATION AND THE PERSISTANCE OF ALLERGIC SENSITIZATION

For many years immunologists have sought reasonable explanations for the fact that the various forms of allergic sensitization of the skin persist in most patients over a period of many years, often for a lifetime.

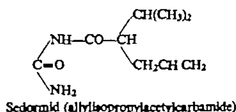
The capacity of infectious micro-organisms to multiply in living tissues, or to survive in small numbers even after clinical cure has been effected, provides a possible explanation for the persistence of allergic sensitivity in some cases (for example, tuberculin reaction, trichophytin reaction, lymphogranuloma venereum reaction). Were this argument valid, it could still not explain the persistence of allergic sensitization to simple chemicals. What maintains these sensitizations to simple chemical compounds, when the patient may have had only a single exposure to the allergen many years before without the remotest possibility of his ever having been re-exposed? The terms "cell memory" (Metalnikov 1928) and "skin memory" (Sulzberger 1940) have been applied to this interesting phenomenon.

One must think only of the minimal exposure which is needed in order to engender deliberate sensitizations to 2, 4-dinitrochlorbenzene—sensitizations which last for many years or for the lifetime of the individual. A minute droplet of a 10 per cent solution of this simple chemical in acetone (approximately 3 milligrams of dinitrochlorbenzene) dropped once on a skin area less than one inch in diameter suffices to bring about lasting sensitization in more than 60 per cent of those exposed. Can a sufficient quantity of the allergen from the single exposure to the minute droplet persist in the human body and maintain sensitization over a period of many years?

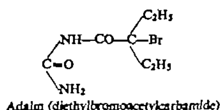
One of the theories explaining the persistence of allergic sensitization, despite lack of re-exposure to the allergen, is based on the possible occurrence of more

the disease were more pronounced after the patient had received sulphathiazole, the primary allergen, than after taking sulphadiazine, the secondary allergen in this case. In a 12 year-old boy with thrombocytopenic purpura due to sulphathiazole reported by Donaldson and Scarborough (1945) even the minute exposure occasioned by an external "patch test" application of an ointment containing 5 per cent sulphathiazole was sufficient to evoke a recurrence of the thrombocytopenic purpura. Moreover a patch test with 5 per cent sulphanilamide ointment produced a similar response, indicating that there was cross-sensitization to this secondary allergen as well. In two cases of purpura haemorrhagica due to neoarsphenamine and in three others due to Bismarsen (Falconer and Epstein, 1940) cross-sensitization to Mapharsen could not be demonstrated.

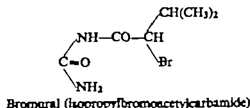
Ackroyd (1948) investigated thrombocytopenic purpura due to Sedormid and remarked that two separate conditions are present in this disease (1) a capillary defect and (2) a deficiency in the number of circulating platelets. The reduction in clot retraction which occurs when Sedormid is added to the blood of patients with Sedormid purpura is, in Ackroyd's opinion, probably also evidence of an effect of Sedormid on the platelets. He was able to demonstrate in one of his patients that two chemically related open chain ureides, Adalin and Bromural, also reduced clot retraction of the blood of patients with Sedormid purpura, although to a lesser degree than did Sedormid the primary allergen. In another of his patients with Sedormid purpura only Adalin had a similar effect.



Sedormid (allylisopropylacetylcarbamide)



Adalin (diethylbromoacetylcarbamide)



Bromural (isopropylbromoacetylcarbamide)

The more severe reaction after exposure to the primary allergen described by Ackroyd in Sedormid purpura and by Hurd and Jacox in sulphathiazole purpura, parallels the situation in cutaneous cross-sensitizations where the primary allergen as a rule elicits stronger reactions than do the secondary allergens.

Another example of probable allergic sensitization affecting an organ other than the skin, which would be interesting to study from the viewpoint of cross

SUMMARY

The potential role of cross-sensitization as a factor which may be involved in the mechanisms leading to persistence of allergic sensitizations for many years and often for a lifetime, despite the complete lack of re-exposure to the compound which engendered the sensitization, is also discussed. It is conceivable that, at least in some instances, exposures to the secondary allergens account for the maintenance of these allergic sensitizations.

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or less permanent changes in the enzyme systems at the sites of protein synthesis (Burnet, 1941) This is thought to lead to the continued formation of altered proteins (antibodies) over a period of many years. If this theory is correct there is no need for attempts to prove the persistence of allergens in the reticulo-endothelial system in order to explain the persistence of allergic sensitization. However if one assumes that the long continued allergic sensitization can be explained only by repeated stimulation due to the persistence of the allergenic material in the reticulo-endothelial system, then one must prove that almost permanent storage of allergens does occur Yet there is no adequate proof for such unlimited storage, although McMaster and Kruse (1951) were able to demonstrate in mice that certain *azo-protein tracer antigens persist* over an astonishingly long period of time.

It may be assumed that in some patients there is more or less frequent exposure to *secondary* allergens over a period of years or for life (Sulzberger 1940). Is it not possible that *it is the often repeated small exposures to secondary allergens* which prevents the sensitization mechanism from becoming extinguished? If this theory were correct, even substances which commonly or regularly behave as elicitors could participate in the maintenance of allergic sensitizations. For it is conceivable that all those substances which lack the capacity of *engendering* allergic sensitizations, but which are capable of *eliciting* allergic reactions, may similarly be capable of *maintaining* allergic sensitization

SUMMARY

Cross-sensitization is the phenomenon where the allergic sensitization engendered by one compound (the primary allergen) extends to one or more other compounds (secondary allergens)

Cross-sensitization is based on the close chemical relationship between two or more compounds, or on the transformation of two or more *previously unrelated* compounds into substances which are related immuno-chemically by conversion in human tissues.

The degree of specificity of each cross-sensitization depends on the more or less frequent occurrence of the determinant chemical grouping. Each and every patient, however develops his own pattern of cross-sensitization which is as characteristic for him as his finger prints

Of the many examples of cross-sensitization which have been studied during the last few decades several are cited. Those which have been most thoroughly investigated and which are discussed in some detail are cross-sensitizations among aromatic amines and cross-sensitizations among local anaesthetics. Because of the greatly augmented opportunities in modern life for exposure to synthetic compounds in contactants, foods, drugs and inhalants, it is pointed out that the discovery of the participating compounds in each cross-sensitization is becoming increasingly complicated.

Cross-sensitizations throw light upon certain hitherto unexplained clinical phenomena Among these are the development of allergic reactions upon *first* exposure to an agent and the persistence of allergic eruptions despite careful avoidance of the causal agent

The future possibilities for application of the cross sensitization concept in allergic processes affecting organs and structures other than the skin are briefly mentioned.

CHAPTER 14

HELMINTHS AND THE SKIN WITH SPECIAL REFERENCE TO ONCHOCERCIASIS AND CERTAIN REACTIONS WHICH ARE LIABLE TO FOLLOW ITS TREATMENT

R. M. Gordon and R. B. Griffiths

INTRODUCTION

Almost any species of helminth parasitic in man may at some stage in its development, cause moderate or severe skin manifestations but the dermatologist who, when confronted with a maculo-papular erythematous rash occurring in a patient known to be harbouring *Trichinella spiralis*, seeks information in an authoritative text-book on parasitology concerning the association, if any between parasite and rash is liable to be disappointed. He may find himself confronted with an account beginning somewhat as follows "Because of the involvement of many organs the protean symptoms of trichinosis resemble those of some 50 other diseases. Five factors determine the variability of clinical symptoms (1) The number of worms (2) the size and age of the patient (3) the tissues invaded (4) the general resistance of the patient and (5) the presence of concomitant pathological conditions. A distinction should be made between zoological and clinical infection" (Belding, 1942). If he further examines the distinction between clinical and zoological infection, he will learn that not less, and probably more, than 10 per cent of the inhabitants of London are harbouring the "pathogenic parasite" *T spiralis* without exhibiting signs or symptoms (Young, 1950). Having read the foregoing account, the dermatologist may not unreasonably wonder why the parasitologist should deem it necessary to consider factors such as the number of parasites and the size of the patient which are not judged relevant by the bacteriologist, and why the parasitologist's account of the association between the parasite and the signs and symptoms should tend to be so much more vague and subject to restrictions than that of the bacteriologist.

This chapter has been written in an attempt to explain some of these differences in approach, and to show why the diagnosis and treatment of skin lesions due to helminth infections must be considered in relation to the life cycle and habits of the parasites responsible.

ASSOCIATION BETWEEN LIFE CYCLES AND HABITS OF UNICELLULAR AND MULTICELLULAR PARASITES AND EFFECTS PRODUCED RESPECTIVELY BY THEM ON VERTEBRATE HOSTS

Before considering the various skin manifestations which may result from helminth infections, it is important to remember that infections caused by multicellular organisms (metazoa), such as the helminths and certain myiasis-producing fly larvae, differ fundamentally from those caused by unicellular creatures, such as

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of the patient's condition may follow chemotherapeutic measures known to be successful in the destruction of the causal organisms. Thus Marmion (1952) suggests that the severe reactions which may follow the successful treatment of typhoid fever with chloramphenicol may be due to the liberation of endotoxin from the killed organisms. Untoward reactions have also been noted following the treatment of leprosy with various potent drugs (Muir 1952) and of syphilis after the use of both arsenicals and penicillin. It is agreed by most authors that these are allergic phenomena associated either with the death of the organisms (Lloyd, 1951), or with an immediate ante-mortem increase in their metabolism (Harrison, 1952). As regards protozoal infections, Stephan and Esquibel (1929) found that a large dose of euflavine (trypaflavine), although successful in removing parasites from the blood of cattle suffering from piroplasmosis, did not prevent the animals from dying, although when treatment was withheld recovery was usual they suggest that the deaths following treatment may have been due to the release of toxins from the dead parasites. Such severe reactions following the successful destruction of the causal organisms by chemotherapeutic measures are rare in most unicellular infections but they are not uncommon in infections due to certain metazoan parasites, and, in the case of some of the filarial infections, the alarming reactions, often involving the skin, which may confidently be expected to follow the successful destruction of a proportion of or all the worm population often cause the physician to hesitate in prescribing a drug which, although efficient as an anthelmintic, has acquired, often quite unjustly a reputation for toxicity

SEROLOGICAL RESPONSE OF VERTEBRATE HOSTS TO INVASION BY UNICELLULAR AND BY MULTICELLULAR PARASITES

At the present time the diagnosis of a large proportion of the diseases caused by bacteria and of a limited number of diseases caused by protozoa can be based with considerable confidence on the results of one or more serological tests. The situation regarding the serological diagnosis of helminth infections, with a few exceptions—such as hydatid disease and trichinosis—is much less satisfactory and in the case of skin lesions suspected of being caused by helminth infections the dermatologist is unlikely to receive much positive assistance from the serologist, although a certain amount of negative information may be made available to him. The reasons for this failure are not far to seek, for reference has already been made to the fact that reactions to helminth infection are usually obtained only after repeated invasions from outside sources and the remarkable changes in form and physiology and the wide anatomical journeys of many of the helminths parasitizing man, render it difficult to prepare an antigen sensitive to all stages of the parasite's development. Finally as pointed out by Wetzel (1952), although the development of antibodies in the vertebrate host against helminths is probably caused by antigens occurring in the secretions and excretions of the parasitic worms, our study of these antigens is hampered because all attempts to culture parasitic worms *in vitro* have failed.

The liability of the human host to become sensitized to the helminth invader will be discussed later it is sufficient to point out here that, for reasons similar to those outlined above, the immunity and allergic reactions developed against the metazoan parasites differ widely from those developed against the unicellular parasites.

protozoa and bacteria In the case of unicellular organisms the number of bacteria or protozoa originally introduced is relatively unimportant since they multiply within the body of the host in the case of the metazoan parasites, however with a few exceptions (for example, *Hymenolepsis nana* in man and rodents and *Probstmayria vivipara* in the horse) no such multiplication occurs and so long as the host fails to develop resistance to the parasites their numbers will be dependent on the magnitude of previous exposures. If in a susceptible individual, the number or intensity of exposures has been great, then the number of parasites will be large, and, if a "pathogenic species" is involved, such infection will normally result in clinical signs and symptoms If on the other hand the number and intensity of exposures have been minimal, then at no stage of the infection will more than a few parasites be present, and those, even if belonging to a "pathogenic species may not produce any clinical manifestations In short in metazoan infections, although the parasite may be present the disease with which it is associated may be absent, even in persons who have developed no resistance or immunity—a state of affairs which is usually referred to as zoological infection and one which is rare in infections with unicellular organisms. Another important distinction between the clinical effects which may be expected to follow invasion by unicellular and by metazoan parasites is related to the fact that the unicellular organisms (with certain important exceptions such as the malaria parasite) follow so to speak, an unplanned cycle of development and while invading the human host do not individually increase markedly in size or regularly alter their habits, so that the general tendency of the bacteria and to a lesser extent of the protozoa, is to cause similar lesions at all stages of their development although of course, the lesions vary in individual cases according to the particular organ which is called upon to bear the brunt of the attack On the other hand, once within the human host many of the metazoan parasites tend to follow a very regular cycle of development, during the course of which they increase very markedly in size and undergo considerable changes in their habits and since such changes are often associated with extensive anatomical migrations the host may be expected to exhibit very different signs and symptoms at different stages of the parasite s development All vertebrates, and for that matter most invertebrates, are liable to become infected with a wide variety of helminth parasites which use their host for one or more stages of their development It so happens that man acts as host to only a very limited number of helminth species (if we exclude rarities not more than 30 species are involved) but these species are distributed among some 13 super families with widely differing life cycles, so that the signs and symptoms produced in the human host may differ very greatly according to the species of helminth involved and as already noted according to the stage of development of that particular species.

EFFECTS ON VERTEBRATE HOSTS OF DESTRUCTION OF UNICELLULAR AND OF MULTICELLULAR PARASITES

In infections with most species of unicellular parasites it is customary to expect that the successful destruction of the invading bacteria or protozoa will be followed by an improvement in the patient s condition. This, however although usual, is not always so and in both bacterial and protozoal infections a worsening

of heavy infections, is negligible. On the other hand, certain species of helminth may rob their hosts indirectly of essential substances, either by draining away a portion of the host's blood (as occurs in man in ancylostome infections), or by interfering with the host's metabolism, either as a result of the parasites producing anti-enzymes to protect themselves against digestion by the host (as is thought to be the case in most alimentary helminthiases) or by actually depriving the host of accessory food factors, as was demonstrated by Bonsdorff and Gordin (1952), who showed that *Diphyllobothrium latum* in the human host absorbed vitamin B^{12} which possibly accounts for the anaemia syndrome in some patients harbouring the fish tape-worm.

As a result of secondary infections being made possible by preceding helminth invasion

The death of such tissue-invading adult helminths as the filariae, particularly *Wuchereria bancrofti* is sometimes followed by the development of an abscess which is usually associated with the growth of bacteria (Anderson, 1924). A similar secondary invasion by bacteria may complicate the dermatitis commonly referred to as "ground itch" which results from the invasion of the skin by the larvae of ancylostomes or other helminth larvae capable of piercing intact stratum corneum the gross ulceration of the skin caused by the guinea worm, *Dracunculus medinensis*, is invariably complicated by secondary infections which may produce serious symptoms if the worm dies or is killed in the deeper tissues.

In veterinary helminthology examples of association between the invasion of the host by helminths and subsequent bacterial infection are well recognized for example, it is known that in the case of the filarial parasite, *Onchocerca cervicalis* which occurs in the ligamentum nuchae of horses, there is sometimes a concomitant *Brucella abortus* infection in the same site (Steward, 1935). Recently Le Roux (1950) has drawn attention to a similar association between *Br. abortus* and another filarial infection, *O. gutturosa* in cattle

As a result of occurrence of parasite in an abnormal anatomical site

The cycle of a particular species of helminth in the well-adapted host generally follows an orderly sequence of events but occasional aberrations are bound to occur and the parasite finding itself in its wrong environment although in its normal host reacts unpleasantly *on the host*, a situation exemplified in the case of the ubiquitous helminth parasites *Ascaris lumbricoides* and *Enterobius vermicularis* or when ova of *Schistosoma haematobium* destined for the bladder find their way into the skin and there cause a dermatitis (Black, 1945).

When a parasite finds itself in a refractory host deviations from its normal anatomical journey become more pronounced. The larvae of *Taenia solium*, escaping from the egg and piercing the gut wall of the pig confine their development to the muscles, with little effect on the host's health but if they find themselves in the human host, in addition to invading the muscle they show a tendency to become aberrant and cause small easily palpable "tumours" under the skin also they commonly parasitize the nervous system and may then destroy the host and incidentally themselves Another interesting example concerns the development of the ruminant liver fluke, *Fasciola hepatica*, in the human host. Although in man this species is capable of completing *its life* cycle in the liver which is its

STATE OF OUR KNOWLEDGE CONCERNING MEANS BY WHICH HELMINTH PARASITES PRODUCE THEIR ILL EFFECTS

At the present time although we have considerable knowledge of the life cycle and habits of the various worms parasitizing man we are surprisingly ignorant of the method by which the different species produce their pathogenic effects indeed, it is true to say that if we omit lesions due to mechanical trauma the cause of other manifestations is usually obscure

Whereas medical helminthology which involves the study of a very limited number of species is a subject of great importance only in the tropics, and then only in the more backward regions, veterinary helminthology which is concerned with the many hundreds of species which parasitize domestic animals is a subject of the greatest economic importance throughout all civilized countries. Indeed owing to over population leading to increased parasitization it is a more serious problem in highly civilized communities than it is in those which are sparsely inhabited and comparatively uncivilized As a result more attention has been concentrated on veterinary than on medical helminthology and much of the very limited knowledge we now possess of the effects of helminths on the vertebrate host is based on veterinary research If we combine our admittedly inadequate veterinary and medical knowledge, the results may be very briefly summarized somewhat as follows. Worm infestations in any vertebrate hosts may on occasions produce serious illness, but in most helminth infections, as in most other parasitic infections, whether caused by unicellular organisms or metazoa it is to the disadvantage of the parasite to cause any disabling injury to the host the ideal relationship being illustrated by Van Beneden s (1889) definition, "A parasite is he whose profession it is to live at the expense of his neighbour and whose only employment consists in taking advantage of him but prudently so as not to endanger his life He is a pauper who needs help lest he should die on the public highway but who practises the precept—not to kill the fowl in order to get the eggs It might be argued however that certain helminth parasites can only continue their life cycle as the result of the death of their host but this is true only of the very limited number of parasites which do inevitably kill their hosts, even in light infections, such as the larval *Multiceps multiceps* which occurs in the brain of ruminants This, however is an exception and in general when serious injury to the host occurs it usually results from overcrowding of a particular species of helminth in a host which has not yet become well adapted to the species Given the presence of these two factors, almost any species of parasitic helminth may produce, on occasions, serious signs and symptoms in the human host The ill effects which may be produced under these circumstances are obvious, but their cause is obscure and in spite of much research is still the subject of controversy Nevertheless, most authorities are agreed that the pathogenicity of parasitic helminths can usually be traced to one or more of the following causes.

As a result of parasite directly or indirectly depriving host of some necessary food supply

At one time it was commonly believed that certain helminth parasites, particularly cestodes, deprived their host of food necessary for his well-being but nowa days it is considered that the amount of food thus directly removed even in cases

Lesions due to helminths and caused by obstruction alone are of very rare occurrence in man we might quote, as examples, intestinal obstruction due to a mass accumulation of adult *Ascaris* or the occasional blocking of the bile-duct by the same parasite. In animals, mechanical obstruction occurs more frequently

Lesions caused by trauma alone occur both in man and in animals with greater frequency indeed, the larval stages of some of the commonest intestinal helminths of man, such as those occurring in the genera *Ascaris*, *Ancylostoma* and *Strongyloides*, which undergo an extensive migration through the body primarily by way of the circulatory system, during their passage through the lungs break out into the alveoli and cause traumatic damage (Plate II, Fig. 1). The penetration of a few of these minute larvae through the pulmonary parenchyma is unlikely to produce serious effects, but if they occur in large numbers the resultant trauma may be extensive and cause various pulmonary lesions.

Another example of uncomplicated trauma of a different nature caused by a helminth parasite in the human host is afforded by the development of the hydatid cyst, the ill-effects of which appear to be largely dependent on the increasing pressure of the cyst on the cells of the invaded organ.

We could add more examples to this list of instances in which the deleterious effects of parasitism can be ascribed either to mechanical obstruction or to trauma. On the whole, however it may be stated that the ill-effects associated with the presence of helminth parasites are more often due to the combined effects of obstruction and trauma. Moreover there are many helminth infections where such combined effect is complicated by other factors, for example, when man is infected by the blood-inhabiting flukes (schistosomes) which lay their eggs in the blood vessels of the recto-vesical plexus, the lesions which follow infection result partly from mechanical obstruction by the worms, partly from traumatic damage caused by various stages of the trematodes, and partly from other factors such as toxic excretions. Similarly the adult forms of *W. bancrofti* the most widely distributed filarial infection of man, inhabit the lymphatics and, by obstructing these vessels, cause elephantiasis, though this is a relatively late manifestation in the course of the disease, and some cause other than mechanical obstruction alone must be found to account for the lymphangitis, "filarial fever and urticaria which often characterize the earlier stages of the infection.

As a result of an allergic reaction consequent on host having become sensitized to some constituent of parasite

It is becoming increasingly apparent that many of the ill-effects associated with the presence of helminth parasites are due to sensitization of the host to some secretion or excretion of the parasite, and that the responsibility for their occurrence is that of the host rather than that of the parasite. Sometimes the association is clear-cut, for example, the dermatitis known as "swimmer's itch" which follows the repeated invasion of the cutaneous tissues by the skin-penetrating non-human schistosome cercariae is unquestionably an allergic manifestation, and there is little doubt that the violent reactions, usually involving urticaria and pruritus, following the death of certain tissue-invading worms is of a similar nature. For similar reasons, it seems probable that the urticarial rash which often accompanies filarial infections,

normal site, nevertheless the fluke not uncommonly becomes aberrant in its wanderings and may be found in the lungs or the skin, where it causes small subcutaneous cysts (Neghme and Ossandon 1943) Again the larvae of the hook worms *Ancylostoma brazillense* and *A caninum* which are normally parasites of carnivores, finding themselves in the human host make no attempt to pursue their normal life cycle, but wander aimlessly beneath the skin, a proceeding which results in the "wandering eruption" well known to most dermatologists with experience of the tropics (Fig. 45)

As this review primarily concerns the skin, it is pertinent to refer to an intractable dermatitis in horses known as "summer sores" and caused by helminth parasites belonging to the genus *Habronema* Normally these worms inhabit the horse's

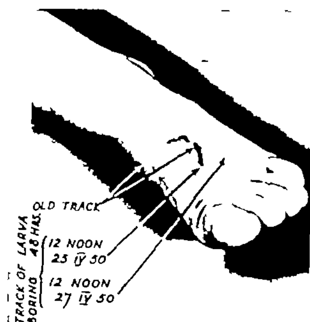


Fig. 45 —"Wandering eruption" occurring in a European child who contracted the infection in South Africa. The track of the larva, probably *Ancylostoma braziliense* has been outlined in Indian Ink and shows the rate of progress made during 48 hours. (*By courtesy of Dr D R. Seaton*)

stomach to which they gain access either by the ingestion of certain infected flies which are the vectors or by the larvae being licked off the skin after deposition Sometimes however the larvae are deposited by the fly on skin wounds inaccessible to the horse's tongue and in such cases the larvae do not develop further but remain in the cutaneous tissues, which react to their presence with the production of characteristic lesions

As a result of mechanical obstruction or trauma caused by parasite

The most obvious and best understood pathological effects produced by certain worm parasites are due, in the first place to mechanical obstruction, usually of the circulatory system particularly of the lymphatics, but occasionally of the gut and in animals of the respiratory tract and in the second place, to direct trauma



Fig 1 — Wandering eruption and urticaria persisting for 6 years and occurring Europea patient suffering from *Strongyloides* nfection hich he had acquired n prisoner-of war camp the F r East (*By courtesy of Dr A R D Adams.*)



Fig 2 — Gener lized eruption persisti g for 2½ years nd occurring in European patient suffering from *Loa loa* infection. Treatment th Banocide caused an ggra ation of the eruption for 2 days, after hich time it anished and after one year observ tion there has been no return of the condition. (*By courte of Dr A R D Adams*)

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PLATE II

such as that caused by *Loa loa* is of an allergic nature—a view supported by the fact that successful destruction of the worms is followed by a temporary worsening of the condition (Fig. 46) (Plate II Fig. 2)

On other occasions however the association is doubtful thus the cause of the intense pruritus occurring in some patients with *Enterobius vermicularis* infection (a reaction which is obviously to the benefit of the parasite since it leads to auto-infection) is not known although its occurrence in only a proportion of patients suggests that it is due to sensitization by the patient rather than to the production of an irritating substance by the worm We have already made reference to the fact that "swimmer s itch is generally due to previous sensitization but certain species of cercariae which are incapable of completing their development in the human host may produce a dermatitis in persons not previously exposed to their



FIG 46.—Calabar swelling occurring on dorsum of left hand of a European patient suffering from a *Loa loa* infection. Within 48 hours of its onset swelling and oedema had completely disappeared. (*By courtesy of D A R D Adams*)

attacks and the reaction in such cases is presumably due to directly irritating substances present in the salivary glands of the larvae These are two examples amongst many in which it is difficult to decide whether the reaction is due to sensitization or to the excretion of poisonous substances such as those considered in the next section

As a result of a poisonous substance usually referred to as a toxin, being produced by the parasite

Certain text-books of general medicine ascribe the ill-effects which follow helminth infections to the production of toxins by the worms. It is true that the presence of substances poisonous to the human host have on occasions, been demonstrated in a few species such as *Trichinella spiralis* *Dracunculus medinensis* (Fig. 47), *Ascaris lumbricoides* and possibly *Schistosoma spp* but it must be acknowledged that the significance of such poisonous substances is incompletely



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FIG —Gener lized eruption persisti g for 2½ years and occurring in European patient suffering from *Loa loa* infection Treatment with Banocide caused an ggra ation of the eruption for 2 days, after which time it vanished and after one year observation there has been no return of the condition (*By courtes of Dr A R D Adams*)

PLATE II

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understood for as Von Brand (1952) has pointed out, there is a difficulty in differentiating "direct verminous intoxication that is, intoxication due to chemical compounds present in or excreted by the worms, and an indirect action" He gives as an example the toxic symptoms which may appear during the migration phase of *T spiralis*, the association of which with a maculo-papular erythematous rash we have referred to previously the toxic symptoms, he suggests, are more likely to be caused by flooding of the body with degeneration products of muscle fibres destroyed during the migratory phase of the helminths than by toxic products of the worms themselves. Such a mechanism may explain some of the effects of somatic helminths. It would appear however that in many helminth infections the reactions which are commonly said to be due to the production of toxins might be ascribed equally well to allergic manifestations.



FIG 47—Ulceration resulting from infection with *Dracunculus medinensis* portion of the protruding worm is being supported on the brush (*By courtesy Dr D R. Seaton.*)

We began this article with the statement that almost any species of helminth parasitizing man may at some stage in its development elicit moderate or severe skin manifestations. We have commented on some of the ways in which the parasite is believed to produce its injurious effects, and we have pointed out that these ill-effects will vary not only with the density of the parasites and the degree of adaptation between the host and the parasite, but also with the species of parasite concerned and the stage of its development in the human host. If these views are accepted, it is clearly useless for the parasitologist to try to associate the wide varieties of parasitic helminths known to produce skin lesions with any particular dermatological manifestation It *might* be of interest, however to select a group of helminths which are particularly associated with skin lesions, to consider one species in some detail as regards its life cycle and habits, and to describe the pathological changes which the dermatologist might expect to correspond with the parasite's development.

SKIN LESIONS IN HUMAN HOST AS EXEMPLIFIED BY *ONCHOCERCA VOLVULUS* INFECTION

Incidence

Onchocerciasis is caused by various species of filarial worms belonging to the genus *Onchocerca* the larvae of which occur in the skin and the adults in the subcutaneous and other tissues of the vertebrate host the worms are transmitted from host to host by different species of biting flies in which the larvae taken up by the insect can develop to the infective stage.

Onchocerciasis in the zoological sense, has an almost world wide distribution and occurs in numerous species of mammals. In Great Britain, for example onchocerciasis is known to occur in both horses and cattle. In horses, the species concerned is *O cervicalis* which is transmitted from animal to animal after the larvae have developed in the common biting midge, *Culicoides nubeculosus* and in cattle the species is *O gutturosa* which completes its development in the "black fly" *Simulium ornatum* Very little is known regarding the pathogenicity of these infections in domestic stock in Great Britain and it is only within recent years that their wide distribution and the high proportion of domestic animals affected has been recognized in Great Britain How frequent is the occurrence of equine onchocerciasis is shown by the work of Le Roux (personal communication) who found a high percentage of horses in the London area infected with *O cervicalis*, and of Steward (1935) working in Herefordshire who examined 53 horses suffering from a fistulous condition of the *ligamentum nuchae* and found 38 to be infected with *O cervicalis* That onchocerciasis in animals may be associated with skin lesions, as will later be shown to be the case in onchocerciasis in man is suggested by the work of Dikmans (1948) who described skin manifestations of a pruritic nature in horses infected with *O cervicalis*

Geographical distribution

Human onchocerciasis is much more limited in its geographical range and is confined to Mexico Central America and tropical Africa In the New World the disease occurs in fairly circumscribed areas, at altitudes of between 1,500 and 5 000 feet where, although restricted in range, it is a common and crippling disease. Thus in the coffee estates in Guatemala, which are situated between 2,000 and 3 000 feet above sea level some 40–60 per cent of the inhabitants are infected while in Mexico it is calculated that there are at least 20 000 cases in Chiapas, one of the three most heavily infested states. In Africa onchocerciasis extends along the coast from Sierra Leone and Liberia through the Gold Coast, Dahomey Nigeria and the Cameroons to the Congo and then to the Southern Sudan Uganda, Nyasaland and Kenya It is not possible to give an estimate of the number of cases occurring in that vast area but in the more intensely infected villages at least 50 per cent of the adult population show the effects of the disease These facts concerning the distribution and prevalence of human onchocerciasis are mentioned in order that the dermatologist may realize that it is a common disease which occurs in vast areas of both the Old and the New Worlds, indeed Stoll (1947) has estimated that some 20 million persons in all are infected with *O volvulus*

In both America and Africa the adult worms occur in subcutaneous nodules, and the larvae or microfilariae produced by the female inhabit the lymph spaces in the skin from which site they can only continue their life cycle if taken up by

biting flies of the genus *Simulium*. At one time it was believed, and certain authorities still hold the view (Brumpt, 1949), that onchocerciasis in the New World is caused by the helminth parasite *O caecutiens*, and in the Old World by *O volvulus*, and that the two parasites differ morphologically and are responsible for different signs and symptoms, especially as regards skin lesions and involvement of vision. Nowadays, however it is generally agreed that *O caecutiens* is a synonym of *O volvulus*, and that the clinical differences observed in patients are due to variations in the intensity of individual infections and, possibly to different strains of the same species of parasites causing different reactions

Life cycle of causal parasite

It is not proposed here to write an account of onchocerciasis as it occurs in man, for excellent and concise descriptions of it will be found in standard works on tropical medicine, such as those by Manson-Bahr (1950) and Brumpt (1949) but rather to recount briefly the life cycle of the causal parasite and to draw attention to the skin manifestations, often of a very dissimilar character which may be traced to various stages of the worm's development in the human host, and to the exacerbation of symptoms which may follow the death of the worms.

For this purpose we may begin our study of the life cycle at the time the microfilariae are taken up by the feeding female fly In order to obtain its blood meal the fly tears the skin with the rasping teeth concealed in the proboscis and at the same time moistens the wound with fluid discharged from the salivary glands. It is during this early stage of feeding that the microfilariae in the lymph spaces are sucked up and pass into the gut of the fly The depth of the wound is now increased until the cutis vera is reached, blood vessels are severed, and the fly is enabled to complete its meal. The resultant abrasion, although tiny is relatively wide and this, combined with the fact that an anticoagulant is injected, causes the blood to continue to flow after the insect has finished feeding and results in the formation of dried scabs of blood on the exposed skin surfaces, a characteristic picture in *Simulium*-infested country The effects of the wounds thus inflicted are of course, trivial when caused by a few flies biting a normal person but when, as is often the case in certain countries, vast numbers of flies combine in the attack, the results may be serious for both man and beast. Ciurea and Dinulescu (1924) record that more than 16,000 cattle died in Roumania in 1923 from the bites of *Simulium reptans* while the serious economic loss resulting from interference with outdoor activity caused by mosquitoes and *Simulium* during the short summer season in Northern Canada, emphasizes the importance of black-fly attacks on man (Twinn, 1950). These severe reactions, which usually develop only after repeated exposures and are probably allergic in character appear to be unconnected with the invasion of any parasite, since they occur equally commonly after bites from uninfected flies as after bites from infected ones, and we mention them only in order to draw attention to the importance of distinguishing the skin reactions due to the saliva of the biting *Simulium* from the papular dermatoses associated with the presence of microfilariae in the skin (Loewenthal, 1943), and also from the reactions which may follow the introduction of the infective form of the parasite by the same species of fly As regards the last, it is possible that persons may become sensitized to the invasive forms of *O volvulus* and their skin may react violently to any fresh invasion by the infective form a reaction which would be

quite independent of—although it might be masked by—the previously described reaction to the fly's saliva We know that such a skin reaction does occur against the invasive stages of several species of helminths, but we have no evidence for or against its occurrence in the case of the filaria infections.

We may continue the life cycle now at the stage where the feeding fly takes up the larvae at this stage the latter measure about 250 μ in length and are invisible to the naked eye The larvae bore through the gut wall and make their way to the thorax of the insect, from which site, after a short resting period during which they undergo several moults they migrate to the head of the fly and enter the *labium* a membranous sheath, which encloses the biting mouthparts of the insect The larvae in the labium, which at this stage of their development measure about 800 μ in length and are just visible to the naked eye have now reached the infective form and are capable of completing their life cycle if they can gain access to a suitable mammalian host. Up to the present no convincing proof of a vertebrate reservoir other than man has been established though that does not mean that no other reservoir exists, for the search has not been extensive and it is possible that further investigations will show that the infective forms are capable of full development in hosts other than man

If the now infective *Simulium* alights and feeds on any warm-blooded creature, the imprisoned larvae burst through the membranous sheath of the *labium* which is in direct contact with the biting mouthparts, and by entering the abrasion made by the feeding *Simulium* gain entrance to the host's deeper tissues if the host happens to be man development proceeds

Once within the human host the tiny larvae develop rapidly and within 9 months to a year have become adult the male measures about 5 centimetres, and the female from 30 to 60 centimetres, both sexes being threadlike and not measuring more than 2–3 millimetres in diameter The adult male and female worms live in the subcutaneous tissues of the human host and most commonly occur in nodules or cysts, where they occupy endothelial lined channels which are probably dilated lymph vessels. In these sites the gravid females, which occur in tangled masses, produce an endless flow of eggs containing fully developed larvae which hatch almost immediately and make their way to the lymph spaces in the skin. The microfilariae of *O volvulus* like those of certain other species of filariae parasitizing man are probably long-lived and Ridley (1945) records their presence in the anterior chamber of the eye 8 months after all discoverable adults had been removed by surgical operation Although they are long-lived the microfilariae undergo no further development in the human host and must eventually perish unless they are taken up from the skin by some species of biting fly of the genus *Simulium* when this occurs the larvae immediately begin to develop and the life cycle is repeated

Signs and symptoms

Although we have considerable knowledge of the development of *O volvulus* in the insect host and although we possess some understanding of the behaviour of the adult worms and of the escape and movements of the larvae produced by them nevertheless, we know very little concerning the life cycle of the worms during their development in the human host, a comment which applies to all species of filaria. What little knowledge we do possess suggests that the migration of the

immature males and females takes place, in the case of *O. volvulus* along lymphatic channels, and that some of the signs and symptoms we are about to describe as being associated with the presence of adult worms may also be observed when only developing forms appear to be present.

Of these manifestations, although the first symptom noticed by the patient is usually pruritus, characteristic subcutaneous nodules are generally the first sign of infection. The onchocercal nodules or bumps as they are sometimes called, vary in size from a pea to a walnut; they may occur anywhere on the body but in Africans they are commonly situated along the pelvic girdle, the iliac crest being one of the most favoured sites. Amongst Europeans and the indigenous population of the endemic areas of the New World the upper half of the body is more commonly involved, a fact which may be related to differences in clothing. On palpation, it will be noticed that the nodules have a firm, rubbery consistency; they may or may not be lobulated, and, although sometimes attached to the deep fascia, the skin above them is freely movable.

The nodules, the most obvious manifestation of onchocerciasis, although unsightly, are seldom a source of complaint, since they are not tender and generally do not lead to any complications obvious to the patient. On the other hand, associated with and not uncommonly occurring before the appearance of the nodules is a persistent and often maddening pruritus which commonly results in scratching and secondary infections. This itching is often the only symptom noted by the patient during the incubation period. It usually persists throughout the infection, although in the later stages of a chronic case it may be absent. It is often accompanied by a peculiar form of dermatitis which is fully described by various authors, notably D'Hooghe (1934, 1935), and Strong (1938).

General signs and symptoms during the early stages of the disease include transient urticaria and a raised eosinophil count, there is a slightly raised temperature, insomnia, itching and slight thickening of the skin. Later the skin becomes wrinkled and shows multiple small creases; palpation reveals general loss of skin elasticity and some residual areas of irregular thickening, of the *peau d'orange* type (Fig. 48).

Although in onchocerciasis the presence of nodules is the most characteristic sign, these lesions often do not form, even when microfilariae are present in the skin. On the other hand, although cases do occur in which no signs and symptoms of the disease can be detected, it is unusual to find a person infected with *O. volvulus*, as evidenced by the presence of microfilariae in the skin, who does not complain of pruritus and/or whose skin shows none of the abnormalities including nodules which we have described.

Treatment

As regards treatment, we shall make reference to chemotherapy in more detail later, but at this point we can state that since it appears certain that the adult forms of *O. volvulus* alone are responsible for the formation of the nodules, and since at this stage, the contained worms are not susceptible to Hetrazan although the drug is capable of destroying the microfilariae, treatment with Antrypol, which has no effect on the microfilariae but destroys a proportion of the adult worms, must be adopted. Surgical removal of the nodules, which is a relatively simple operation, is sometimes recommended in cases where the tumours occur on the scalp. This

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The nodules, the most obvious manifestation of onchocerciasis, although unsightly are seldom a source of complaint, since they are not tender and generally do not lead to any complications obvious to the patient. On the other hand, associated with and not uncommonly occurring before the appearance of the nodules is a persistent and often maddening pruritus which commonly results in scratching and secondary infections. This itching is often the only symptom noted by the patient during the incubation period. It usually persists throughout the infection, although in the later stages of a chronic case it may be absent: it is often accompanied by a peculiar form of dermatitis which is fully described by various authors, notably D'Hooghe (1934–1935), and Strong (1938).

General signs and symptoms during the early stages of the disease include transient urticaria and a raised eosinophil count, there is a slightly raised temperature, insomnia, itching and slight thickening of the skin. Later the skin becomes wrinkled and shows multiple small creases: palpation reveals general loss of skin elasticity and some residual areas of irregular thickening, of the *peau d'orange* type (Fig. 48).

Although in onchocerciasis the presence of nodules is the most characteristic sign, these lesions often do not form, even when microfilariae are present in the skin. On the other hand, although cases do occur in which no signs and symptoms of the disease can be detected, it is unusual to find a person infected with *O. volvulus*, as evidenced by the presence of microfilariae in the skin, who does not complain of pruritus and/or whose skin shows none of the abnormalities including nodules which we have described.

Treatment

As regards treatment, we shall make reference to chemotherapy in more detail later: but at this point we can state that since it appears certain that the adult forms of *O. volvulus* alone are responsible for the formation of the nodules, and since, at this stage, the contained worms are not susceptible to Hetrazan although the drug is capable of destroying the microfilariae, treatment with Antrypol, which has no effect on the microfilariae but destroys a proportion of the adult worms, must be adopted. Surgical removal of the nodules, which is a relatively simple operation, is sometimes recommended in cases where the tumours occur on the scalp. This

recommendation is given because it is believed that microfilariae migrating from such nodules threaten to involve the eyesight but nowadays this practice is seldom adopted as a routine

Although the nodules are caused by the adult worms, the pruritus and rash are apparently due to the presence of the microfilariae in the skin, and persist for long periods after the removal of all nodules containing adult worms. As might be expected therefore treatment by Hetrazan which destroys the larvae, eventually relieves the pruritus but as might further be expected from a knowledge of the life cycle, the pruritus and skin lesions will inevitably return unless therapeutic measures against the microfilariae are combined with measures designed to destroy the



FIG 48 —Onchocerciasis occurring in an African patient. The photograph shows an onchocercal nodule on lateral aspect of thorax. There is a moderately severe onchocercal dermatitis of many years duration and wrinkled skin, typical of this stage of the condition, can be seen. There was a general loss of skin elasticity and some areas of irregular thickening of *peau d'orange* type could be palpated. (*Photograph by courtesy of Mr G R. Barnley Description of case by courtesy of Dr G S Nelson*)

adult worms moreover it should be recognized that if surgical measures are employed they may have to be repeated possibly more than once, to remove worms which have reached maturity subsequent to the first operation

We have referred to the fact that the journeyings of the developing worms in the human host are probably along lymphatic channels and although onchocerciasis, unlike certain other filarial infections, is not typically associated with elephantiasis, nevertheless elephantiasis is sometimes a complication which when it occurs, generally involves the genitalia and is often associated with hydrocele, microfilariae being present in the fluid It is probable, although not proved that blockage of local lymphatics by immature worms or by aberrant adult worms is the cause of this complication hence, chemotherapeutic treatment with Antrypol is preferable to the giving of Hetrazan In this connexion however it is important to remem-

ber that in Africa *W. bancrofti* the adult form of which is to some extent susceptible to Hetrazan, is often associated with *O. volvulus* and that in mixed infections *W. bancrofti* is the more likely culprit.

The most serious complication of onchocerciasis is unquestionably the involvement of the eyes, which often leads to complete blindness, usually associated with punctate keratitis and lateral formation of pannus. It is only within recent years that such eye conditions have received expert attention, and some of the earlier reports probably included patients who although infected with *O. volvulus* were suffering from eye conditions attributable to other diseases thus, Ridley (1945) who, in an investigation in West Africa, examined 300 persons and found "61 had serious eye diseases, 51 ocular onchocerciasis, including 22 who were below British blind certification standards and 11 trachoma is careful to point out that amongst the people examined signs of vitamin A deficiency were practically universal." Similarly Sarkies (1952), also an eye specialist working in West Africa, who examined 319 proven cases of onchocerciasis and found that 109 (34 5 per cent) showed some lesions of the eye which could be attributed to the onchocercal infection notes that some of the cases benefited from riboflavine administration. Although caution must be observed in attributing eye lesions in patients with onchocerciasis to the effects of the helminth parasites, nevertheless, all authorities are agreed that in any area where onchocerciasis is prevalent both in the Old World and in the New this disease is responsible for a high proportion of serious eye lesions, including blindness, occurring in the area (Strong, 1938), and that as many as 73 per cent of the population may have nodules, 43 5 per cent may have eye lesions and 10 per cent of the population may be blind (Hissette, 1932).

During recent years considerable attention has been paid to the pathology of onchocercal blindness, and as a result of those investigations there seems little doubt that the lesions responsible for the blindness are caused, not by the adult worms but by the microfilariae, although we do not know by what means the latter produce their harmful results. Ridley writing as recently as 1945 on the treatment of such cases, remarks "It must be confessed that so far there is no effective treatment for no drug is known which will kill any form of *microfilaria* without endangering the life of the host During the past 5 years the eagerly awaited discovery of a drug capable of curing the patient of onchocerciasis appeared to have been made on two occasions. The first occasion was when van Hoof and his colleagues (1947) announced that Antrypol (naphuride sodium) destroyed the adult *O. volvulus* worms and caused many of the microfilariae to disappear from the skin These observations were confirmed by subsequent workers but, further investigations showed that although Antrypol reduced the number of microfilariae it never eradicated them, nor could it be relied upon to destroy *all* the adult worms. Hopes were again raised when Hewitt and his fellow workers (1947) published their discovery that a new filaricidal drug Hetrazan (one of the piperazines) was effective in treating rodent filariasis and when, a little later it became established that the same substance caused a fairly rapid disappearance of the microfilariae of *O. volvulus* from the skin, many workers believed that the problem of onchocerciasis had been solved. At first it was supposed that Hetrazan was also capable of destroying the adult worms in the nodules, but further investigations proved that it had no rapid effect on the adult worms, although a proportion were destroyed by prolonged treatment.

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reacts with skin or other manifestations to a varying extent depending upon the degree of adaptation which has been achieved. The degrees of adaptation may be grouped as follows. (1) Complete refractoriness, in which the parasites cannot undergo any development man is constantly exposed to invasion by certain helminth parasites which cannot undergo any development in the human host. (2) Partial refractoriness, in which parasites can undergo incomplete development in such cases the pathological effects are often pronounced for example, many of the skin-piercing larval stages of flukes and nematodes of animals, having successfully passed the skin barrier in the human host, undergo no further development and perish but before doing so they may evoke severe skin lesions. (3) Developing adaptation between host and parasite, in which helminth parasites are able to develop completely in man, but where complete adaptation between host and parasite is not achieved and more or less pronounced lesions may develop—as for example, in most filarial infections. (4) Complete adaptation, in which a state of balance between host and parasite has been reached and disease only occurs when this equilibrium is upset. In the case of man such a state of equilibrium has been reached only by a very limited number of helminth species.

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The final result as it stands today is that in Antrypol we possess a moderately efficient drug for the destruction of the adult forms of *O volvulus* and in Hetrazan a highly efficient anthelmintic for the destruction of the microfilariae hence it might be thought that the employment of these two drugs might lead to a rapid cure of the infection This is true up to a point but unfortunately the employment of either Antrypol or Hetrazan in the treatment of onchocerciasis is liable to be followed by severe reactions such as an almost intolerable pruritus, urticaria and ocular changes, including temporary blindness, which cause a proportion of patients to refuse treatment or to leave hospital without completing the course. With both Antrypol and Hetrazan the severity of the reactions are proportionate to the intensity of the infection but in persons with equal intensities of infection, Hetrazan produces a much more violent response than Antrypol. At first there was a tendency to ascribe these ill-effects to the poisonous character of the drugs and suggestions were made regarding the necessity of finding a so-called less toxic drug. It was soon realized, however that these side-reactions were not connected with any toxicity of the drug since they occurred even with doses well tolerated both by normal persons and by patients with *W bancrofti* infections. In view of these findings it is now generally recognized that severe reactions occurring in patients with onchocerciasis who have been treated with Antrypol or Hetrazan are due to the death of the microfilariae and to a lesser extent of the adult worms, resulting in the release of antigen in a previously sensitized patient Modern therapy therefore, consists in the administration of either or both drugs in cautious doses and in relieving manifestations of allergy by the administration of anti histaminics.

CONCLUSION

Earlier in this chapter we drew attention to the obvious, but often forgotten, fact that with few exceptions it is to the disadvantage of the parasite to inflict considerable injury or even inconvenience on its host Nevertheless, as we pointed out, many species of parasitic helminths when present in sufficient numbers may cause serious or even fatal disease in man and other animals. Later we analysed the means by which some of these injuries are produced and ascribed their occurrence to a variety of causes such as trauma or allergy to mention only two Finally we selected the filarial worm *O volvulus* as an example of an injurious helminth parasite, and discussed the various lesions and reactions which it may produce at different stages of its development in the human host We might equally have selected almost any other helminth infection of man to illustrate the fact that the associations between parasitic helminths and the skin lesions produced in the host are seldom clear-cut or simple, depending as they do not only on the species of parasite concerned but also on the stage of its development and the nature of the exposure which led to the infection for example the skin may be invaded by larvae or it may serve as a habitat for adult worms and in some cases, for their larval progeny or it may react in an allergic manner to the presence of helminths, not only in the skin but also when they occur in tissues or organs remote from the skin structures

Finally the dermatologist must realize that the human host has reached a stage of equilibrium or complete adaptation only to a very limited number of species of helminths and to the remainder although individual susceptibilities exist, he

Staphylococcus pyogenes a considerable amount of information is available. For practical purposes resistant strains of *Staph. pyogenes* are resistant because they produce an enzyme, penicillinase, which destroys penicillin. The presence of this substance was first demonstrated by Kirby (1944 and 1945) who extracted a potent penicillin inactivator from 7 resistant strains, and numerous workers, including Bondi and Dietz (1945), who first used the term penicillinase to describe it, have confirmed these findings. Initially in the clinical field resistant staphylococci were of considerable rarity and it was not until after some years of penicillin usage that they became sufficiently prevalent to cause alarm. Much of the early work on this aspect was done by Barber who first drew attention to the progressive increase in the proportion of penicillin-resistant staphylococci among the patients of a London hospital. In successive periods during 1946–48 the proportion of staphylococci found resistant was 14 38 and 59 per cent (Barber 1947 Barber and Rozwadowska Dowzenko, 1948). The passage of time has led to no improvement, and there have been reports from many parts of the world showing that when pathogenic staphylococci are recovered from within hospitals 60 per cent or more of them are likely to be resistant to penicillin Resistant staphylococci are much less common among hospital out-patients and presumably the general public A recent report (Birnstingl, Shooter and Hunt, 1952) showed that at one London hospital 16 per cent of the strains isolated from casualty patients were resistant, as compared with 6 5 per cent of staphylococci isolated from similar patients 3 years previously Dermatological and ear nose and throat out-patient departments form an exception, as in these departments resistant staphylococci may be as common as within hospitals.

The mechanism by which resistant strains have developed appears to be one of selection, and not of adaptation. Continued exposure to graded amounts of penicillin will increase the tolerance of an originally sensitive staphylococcus for penicillin, and if this is prolonged the organism may become resistant to fantastically high levels of penicillin, as in the instance reported by Klimek, Cavallito and Bailey (1948) and Bellamy and Klimek (1948) where the organism was resistant to 4 milligrams per millilitre, over 300,000 times the normal. Changes of this sort are accompanied by loss of virulence and by gross alteration in the morphology and cultural characteristics, the resulting bacteria bearing little resemblance to their original parent and this type of resistance is rarely if ever accompanied by penicillinase formation Further the resistance is usually lost on culture in the absence of penicillin. On the other hand, the ability to form penicillinase appears to be a property of resistant staphylococci which they possess irrespective of their previous history and the present resistant strains are the descendants of a small minority of penicillinase producers which by selection have gradually become more numerous. Selection has been most active within hospitals, as in these circumscribed communities where penicillin has been freely used, conditions have favoured the survival of the originally rare resistant strains.

Failure to distinguish between these two types of resistance has led to considerable confusion in the past, and to views on treatment which are now known to be unsound. As all resistant staphylococci encountered in clinical practice are of the naturally penicillinase-forming variety it follows that resistant staphylococci cannot be produced in any one patient by the use of penicillin either in adequate or inadequate dosage. Such use will, however lead to the abolition of sensitive

CHAPTER 15

RECENT DEVELOPMENTS IN THE USE OF ANTIBIOTICS

R. A SHOOTER

BACTERIAL RESISTANCE AND DEPENDENCE

Bacterial resistance

THE last 18 years have seen the development of the sulphonamides and the appear ance of one new antibiotic after another with the result that there are few bacterial infections in which it has not been possible to cure the patient by the suppression of the infecting organism This complete change from an era in which, for infective *diseases of bacterial origin, no form of* chemotherapy was available, to one in which almost every infection is potentially treatable has emphasized the failures that still occur That failures do still happen is due, in the main, to the presence of drug resistant organisms and up till now these organisms have been dealt with by the discovery and application of a new antibiotic This process is presumably not endless and as the development of resistant strains threatens to nullify the value of antibiotic treatment it is worth considering this phenomenon at some length

A warning of what was to come was seen first in the treatment of gonorrhoea with sulphonamides. From the start a small proportion of patients failed to respond, and it was shown by Felke (1938) that organisms isolated from such cases were resistant to sulphonamides while those isolated from cases in which treatment was subsequently successful were sensitive Resistant strains gradually increased in prevalence until Dunlop (1949) was able to report that he encountered *no less than 85 8 per cent of such strains The period when resistant strains* began to be sufficiently numerous to form a real problem in treatment coincided with the introduction of penicillin which provided a practical solution as it did in the case of some of the other organisms which also became resistant. Resist ance to sulphonamides has been admirably outlined by Garrod (1950 and 1951) in the course of reviews of bacterial resistance to chemotherapeutic agents, and he concludes that it must inevitably have seriously impaired the general usefulness of these drugs had they remained our only resource in treating the infections con cerned. Present information as to the distribution of sulphonamide-resistant strains is very scanty and the problem is of little practical importance, but before dismissing it, it is worth observing that the sulphonamides are unique in that their mode of action is known and that this knowledge has simplified the investigation of acquired resistance The mechanism is known to be the formation of a sul-phonamide inhibitor shown in some cases to be *para*-aminobenzoic acid

Lack of precise knowledge of the way in which penicillin and the later antibiotics act has hampered investigations designed to elucidate the development of resist ance, and has gone far to make any attempts to prevent resistance developing purely empirical Penicillin has been longest in the field and for one organism

Staphylococcus pyogenes a considerable amount of information is available. For practical purposes resistant strains of *Staph pyogenes* are resistant because they produce an enzyme, penicillinase, which destroys penicillin. The presence of this substance was first demonstrated by Kirby (1944 and 1945), who extracted a potent penicillin inactivator from 7 resistant strains, and numerous workers, including Bondi and Dietz (1945), who first used the term penicillinase to describe it, have confirmed these findings. Initially in the clinical field resistant staphylococci were of considerable rarity and it was not until after some years of penicillin usage that they became sufficiently prevalent to cause alarm. Much of the early work on this aspect was done by Barber who first drew attention to the progressive increase in the proportion of penicillin-resistant staphylococci among the patients of a London hospital. In successive periods during 1946–48 the proportion of staphylococci found resistant was 14 38 and 59 per cent (Barber 1947 Barber and Rozwadowska-Dowzenko, 1948) The passage of time has led to no improvement, and there have been reports from many parts of the world showing that when pathogenic staphylococci are recovered from within hospitals 60 per cent or more of them are likely to be resistant to penicillin. Resistant staphylococci are much less common among hospital out-patients and presumably the general public A recent report (Birnstingl, Shooter and Hunt, 1952) showed that at one London hospital 16 per cent of the strains isolated from casualty patients were resistant, as compared with 6 5 per cent of staphylococci isolated from similar patients 3 years previously Dermatological and ear nose and throat out-patient departments form an exception, as in these departments resistant staphylococci may be as common as within hospitals.

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Failure to distinguish between these two types of resistance has led to considerable confusion in the past, and to views on treatment which are now known to be unsound. As all resistant staphylococci encountered in clinical practice are of the naturally penicillinase-forming variety it follows that resistant staphylococci cannot be produced in any one patient by the use of penicillin either in adequate or inadequate dosage. Such use will, however lead to the abolition of sensitive

strains whose place may be taken by resistant ones, and it is undoubtedly nothing but the widespread use of penicillin which has led to the great increase in such strains If this could have been foreseen, a case could have been made out originally for the rigorous restriction of penicillin to nothing but the most serious infections. Such a course would plainly have been impracticable even if desirable, and against the infections now untreatable by reason of resistance should be set the enormous amount of ill health which has been prevented To quote one minor illustration patients with carbuncles were commonly admitted to hospital wards, something which now is rarely necessary this is a change which is hardly attributable to anything other than the early use of penicillin and the newer antibiotics. These studies of penicillin resistant staphylococci which have also shown the great and almost unsuspected frequency of cross-infection, have been enormously aided, and indeed have been largely dependent on the serological and bacteriophage methods of typing staphylococci which have become available in the last few years.

For no other species has penicillin resistance become such a pressing problem and for two the gonococcus and Group A β-haemolytic streptococcus, no infections due to resistant strains have yet been seen In the case of the gonococcus this is all the more remarkable as *in vitro* the resistance of this organism to penicillin can be raised with ease

Streptomycin presents an entirely different problem. All bacteria can become resistant to streptomycin both in the test tube and in the body and this resistance, which is permanent may develop with great rapidity Whatever may be felt about the indiscriminate use of penicillin, there can be no doubt that the prescription of streptomycin without adequate indication that it will be effective is very likely to breed resistant organisms. The more streptomycin used, the larger the number of bacteria resistant to it and it is for this reason that it has been suggested that streptomycin should be reserved for the treatment of tuberculosis. The speed with which resistance develops is linked to the rate of bacterial growth for slow growing tubercle bacilli it may take weeks, while others may be resistant in 24 hours and as few organisms grow at the leisurely pace of the tubercle bacillus, for most infections in which streptomycin is used any good that may be done is likely to be done within the first few days of treatment. This is well exemplified in the treatment of urinary infections Streptomycin is rapidly bactericidal (Garrod, 1948) and this property makes it an excellent disinfectant for the treatment of susceptible infections of the urinary tract Treatment need only be of very short duration for if sterilization is not achieved within 2 days, the remaining organisms are likely to have reached such a high degree of resistance as to have gone far beyond the upper limit of any possible therapeutic concentration As a matter of practical interest it should be remembered that streptomycin is effective in an alkaline medium and largely neutralized in an acid one, and that failure to adjust the reaction of the urine to the alkaline side of neutral before treatment is begun is responsible for many unsatisfactory results.

For a short time after the introduction of the broad-spectrum antibiotics hope was expressed that resistance would not develop, but this was soon found to be based on optimism rather than on experience, and in most parts of the world the findings have been that the number of resistant organisms has risen hand in hand with the increased use of antibiotics. Schneierson (1952) reported from America that strains of *E. coli* *Proteus* *Staph. aureus* and *Streptococcus faecalis* resistant

to aureomycin had increased during the previous three years similar findings of an increase of resistant organisms to the broad-spectrum antibiotics were reported from Australia by Thomson (1952), and from France, Chabbert and Terral (1952) described a rise in the proportion of resistant staphylococci, including one series with 23 per cent of staphylococci resistant to all antibiotics.

While figures derived from strains collected within hospitals may be biased by cross infection, there is little doubt that many species of bacteria are developing resistant strains, and that in most cases, once resistance has developed it is permanent. The reason why bacteria become resistant is unknown, but the mechanism resembles resistance to streptomycin in that most species are able to acquire it and it will follow exposure in the test tube or in the body No evidence has been brought forward to suggest the replacement of sensitive strains by ones originally resistant, and for staphylococci no resistant ones could be found in 500 strains collected before aureomycin came into use (Birnstingl, Shooter and Hunt, 1952). Several groups of workers have investigated the behaviour of these newer antibiotics, and from their work a general pattern has emerged. Resistance to penicillin and to streptomycin develops independently and as far as Gram-positive cocci go, this is true of chloramphenicol. With Gram-negative bacilli resistance to chloramphenicol, terramycin and aureomycin is closely linked, and bacteria resistant to one are usually resistant to all three. In the case of terramycin and aureomycin this association also applies to Gram-positive cocci. This last finding is not supported by all the published work on the subject, but as Monnier and Schoenbach (1951) point out, aureomycin is an unstable drug, and organisms found to be sensitive to terramycin but resistant to aureomycin, should be retested to ensure that the aureomycin has not lost its potency A curious accompaniment of acquired resistance in the test tube to the newer antibiotics is that penicillin-resistant staphylococci lose their ability to make penicillinase and thus become more sensitive to penicillin. This response has not yet been seen in patients, nor has it been shown to occur in experimental infections.

The increase of resistant strains outlined here is alarming, and if it continues may go far to reduce the field of usefulness of the present broad-spectrum antibiotics.

Bacteria, like other living creatures, adapt themselves to their surroundings, and when confronted with an antibiotic may respond in a variety of ways. If the antibiotic is a bactericidal one, and is present in sufficient strength, the organism may be killed outright lower concentrations of the same antibiotic, or substitution of a bacteriostatic one, may lead to inhibition of bacterial growth. On the other hand, the organism may be able initially to tolerate the antibiotic by producing a substance such as penicillinase, which will destroy it, or by being frankly insusceptible to its action. If not initially resistant, it may become so either in slow steps, as in the resistance produced by broad-spectrum antibiotics, or by the convulsive bounds which sometimes follow exposure to streptomycin. Other reactions may occur In the course of becoming resistant, the organism may become dependent upon the antibiotic, and incapable of growing without it, or while not being dependent, may be stimulated by low concentrations.

Bacterial dependence

Bacterial dependence was first shown by Miller and Bohnhoff (1947) who described variants of meningococci which were not only resistant to streptomycin

but were not able to grow in its absence, and similar strains have been described for a number of other organisms including *Staph aureus Bact coli Ps procyanea, Bact friedlanderi Proteus* and the tubercle bacillus (Paine and Finland 1948a and b Hobby and Dougherty 1948) This curious response is not entirely confined to streptomycin as Miller (quoted by Garrod 1951) has reported a variant of a meningococcus which required penicillin for growth in a deficient medium but not in a richer one, and Gocke and Finland (1950) described a resistant variant of *Bact friedlanderi* which was dependent on a critical concentration of chloramphenicol. Nor is it purely a laboratory curiosity as it may occur during treatment with streptomycin Miller and Bohnhoff (1949) recovered dependent bacteria from the throats of nurses administering the drug, and such organisms have been found during the treatment of urinary infections (Stenderup 1952) How far dependence is of any importance in determining the outcome of treatment is uncertain, but it is theoretically possible that an infection with a preponderance of dependent organisms might be perpetuated by streptomycin, and it is possibly an additional argument for restricting treatment to the shortest time possible

The stimulation of bacterial growth by low concentrations of antibiotics has been reported by a number of workers. This phenomenon which for technical reasons is not always easy to distinguish from the effects of other factors, usually occurs when bacteria are exposed to a lower concentration of an antibiotic than that needed to inhibit growth. For staphylococci it has been shown to occur in broth cultures with penicillin (Miller Green and Kitchen, 1945) and with the same drug on solid media by Garrod (1951) who also showed that penicillin increased the pigment production and colony size of *Ps procyanea* In the hands of Curran and Evans (1947) low concentrations of both penicillin and streptomycin accelerated the germination of spores, and the growth of staphylococci and streptococci in a skim-milk medium, and more recently Story (1953) has found that subinhibitory amounts of penicillin will enhance haemolysin production by pneumococci The mechanism responsible for this form of bacterial stimulation is quite unknown, although it is plainly closely related to a similar phenomenon seen with many other germicides, and covered by the Arndt Schulz law which stated shortly is *Kleine Dosen reizen grosse Dosen lähmen* or in other words, poisons are stimulants in small doses. However it is brought about the basis of the action is presumably nutritional, and it is interesting that in the laboratory this type of stimulation has been most marked in a deficient medium

The production of larger colonies in the laboratory does not by any means prove that when exposed to the same concentration of the antibiotic under the quite different circumstances in the body bacteria will grow more quickly or be more virulent, and the part, if any played by stimulation in clinical infections is most difficult to assess Subinhibitory concentrations of the kind required to stimulate staphylococci must be present at some time in every staphylococcal infection treated although the necessary concentration will be speedily passed in the rapid rise of penicillin levels immediately after injection and during the longer period when the penicillin level is falling surviving staphylococci are unlikely to be able to respond to any stimuli Possibly a more serious danger may lie in the use of repository forms of penicillin in which blood concentration has been unduly sacrificed for length of action, particularly in the treatment of circumscribed lesions into which penicillin may have difficulty in penetrating, and a similar caution may

apply to too low oral dosage. Organisms possessed of considerable natural resistance to antibiotics may present a different problem, as in their case concentrations normally maintained in the body may be suitable for stimulation. The tubercle bacillus is a case in point, but although there is some evidence, not entirely confirmed, that *in vitro* stimulation of growth can be produced by penicillin, no clear proof has been put forward that this reaction takes place in experimental animals or in tuberculous patients. Indeed, with the exception of the report by Welch, Price and Randall (1946) who found that subcurative doses of streptomycin increased the mortality from *Salmonella typhi* in mice, and that of Randall, Price and Welch (1947) who found the same to be true for penicillin, there is little clinical or experimental evidence that bacterial stimulation takes place in the body

While the foregoing paragraph refers to definite bacterial infections, there is no doubt that something frequently happens during antibiotic therapy which is related, and possibly closely related, to stimulation. The surface of the body and the various cavities communicating freely with the exterior have a bacterial flora of their own, and this flora may be markedly changed by the administration of antibiotics. Long (1947) showed that during local treatment of the mouth and throat with penicillin the normal bacteria were largely replaced with resistant coliform bacilli, and this type of change has been demonstrated in other parts of the body Absence of knowledge of the factors which determine the presence of bacteria in any one situation makes it difficult to interpret these findings. If the normal inhabitants of the mouth compete more effectively for the available food supply or excrete substances inimical to other bacteria, their removal by penicillin and replacement by coliform bacilli can hardly be classed as an example of penicillin stimulation. The same argument can be applied to situations where an infecting organism is replaced by another as may happen in the treatment of infections such as those of the lung or urinary tract. To hold that the appearance of the second organism is due to stimulation would be to maintain that damaged tissue has the ability of normal tissue to remove invading bacteria. Some light may be shed on this problem by a very brief consideration of post-operative chest infection. Whatever may be the cause of this condition, there is general agreement that the initial abnormality is some form of collapse, and once this happens bacterial infection follows quickly If the bacteria are derived from the mouth, as has been suggested (Ellis and Shooter 1952), the nature of the infection will depend on the flora of the mouth, and any changes in this flora due to antibiotics may be reflected in the lungs.

Having stated the case against stimulation, it is only fair to point out that the most likely superinfection to be observed clinically during antibiotic treatment is that due to *Candida albicans*, and for this organism Foley and Winter (1949) have shown that penicillin has a stimulating effect in the test tube and also increases the mortality of infected chick embryos. Woods, Manning and Patterson (1951) and numerous other authors have reported monilial infection as a complication of antibiotic therapy It has been seen following the use of penicillin, aureomycin and chloramphenicol and commonly involves the mouth, vagina and anus. Cases of broncho-pulmonary moniliasis have been reported as have infections of the alimentary tract of the 20 cases reported by Woods and his colleagues 6 had abnormal numbers of monilia in the stools.

The clinical significance of superinfections depends on the virulence of the

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unknown, although theories have been put forward to account for it. Antagonism can be partially accounted for as penicillin is known to act best on actively multiplying organisms, the result of adding a bacteriostatic drug is presumably to slow division, thus tending to remove the bacteria from the influence of penicillin. It is certainly not due to the chemical neutralization of one drug by another.

Although these reactions were first demonstrated in the test tube, there is by now a considerable amount of evidence to suggest that they are not confined to the laboratory but may occur during the treatment of patients. Both can be produced experimentally although for the production of antagonism a narrow dosage scheme must be observed, as an excess of either component will overcome the antagonism. In the clinical field synergism is best seen in the treatment of endocarditis due to penicillin-resistant enterococci with a combination of penicillin and streptomycin. Antagonism has been observed in the treatment of pneumococcal meningitis with penicillin and aureomycin. Lepper and Dowling (1951) who reported this, found that the mortality was 30 per cent in those treated with penicillin alone but was 79 per cent in those who received aureomycin in addition to penicillin.

From a practical point of view it would be gratifying to be able to produce synergistic action, particularly in infections which respond only slowly and it is even more necessary to avoid neutralizing the good effects of one antibiotic with another. Just how likely this is to happen is uncertain. It will be noticed that subacute bacterial endocarditis, in which synergism is best seen, is an infection in which the natural defences of the body are relatively incapable of dealing with invading bacteria by themselves, and in which an effective antibiotic must be able to kill virtually all the invaders. The synergistic effect of streptomycin lies not only in its acceleration of the rate of killing of penicillin, but also in enabling penicillin to kill the last few remaining bacteria, which otherwise in the case of a moderately resistant organism might be left dormant but alive. This is probably not necessary for many other types of infection, and although anything which speeds up the action of penicillin is welcome, the fact that not every organism is killed is immaterial as the patient is able to deal with the survivors.

Attempts to demonstrate antagonism experimentally have required careful designing, as it can be suppressed by an excess of either drug, and convincing evidence of its occurrence in the treatment of any but a few human infections is lacking. In most infections larger doses of antibiotics are used than are strictly necessary and when two are used together there is probably the necessary excess present to prevent undesirable interference, and even if this was not so an only moderate impairment of the action of, say penicillin would be difficult to detect clinically. As Jawetz (1952) points out, in the antagonism reported in the treatment of pneumococcal meningitis the circumstances were ideally suited for its occurrence in that an effective drug was combined with a bacteriostatic agent, and both were present in critical concentrations but without any excess.

Finally it should be observed that ordinary laboratory tests of the sensitivity of bacteria to antibiotics depend on the inhibition of bacterial growth, and these tests reveal nothing of the ultimate fate of the bacteria exposed or whether they have been killed or merely prevented from growing. If this information is required so that the effects of combinations of antibiotics may be observed, more exacting

invading organisms and their susceptibility to other forms of treatment. Invasion by an active pathogen resistant to all antibiotics may be disastrous, and may even give rise to what amounts to a new disease. This has been reported by Jackson and his colleagues (1951) from Boston where, of 91 patients with pneumonia treated with terramycin 7 died in 4 of whom there was a staphylococcal pulmonary infection and in 5 a serious staphylococcal infection of the alimentary tract. This most unusual behaviour on the part of the staphylococcus has been reported again by the same authors following the use of terramycin in the treatment of urinary infections (Womack and his colleagues, 1952) This type of super infection has recently been reported with terramycin from other centres, and even if it represents local cross-infection with one type of staphylococcus, it is perhaps a warning of the new disease patterns which may lie ahead of us.

SYNERGISM AND ANTAGONISM

It was a very natural development that two effective or moderately effective antibiotics should be used together in the hope of producing a better result than followed the use of either singly and combinations of this sort have been widely used. Although theory has not caught up with practice, it is in some cases possible to predict the likely result of using an antibiotic pair Much of this knowledge we owe to Jawetz and his colleagues, whose papers on this subject are summarized in one publication (Jawetz, 1952) Stimulated by the failure of sulphonamides, penicillin streptomycin, aureomycin or chloramphenicol to cure a patient with subacute bacterial endocarditis due to an enterococcus, they were led to investigate the effects of drug combinations on bacteria and in the belief that the killing of micro-organisms rather than their inhibition was essential for the successful treatment of endocarditis, they selected the rate of bactericidal action as the gauge by which to judge their results. Using this method and working with an enterococcus, they found that when penicillin was added to cultures the majority of the bacteria died at a steady rate, but a significant number survived When streptomycin was added to the same amount of penicillin the rate of bactericidal action was greatly accelerated and all the bacteria were killed even though the amount of streptomycin added was so little that alone it would have been ineffective. This process they called synergism The antithesis, antagonism, was demonstrated when they showed that the addition of chloramphenicol to penicillin, even in barely bacteriostatic concentration, greatly slowed the rate of killing, so that after 24 hours more bacteria survived than with penicillin alone

As a result of further work which has been confirmed by other workers, they were able to divide antibiotics into two main groups, the first comprising the bactericidal antibiotics penicillin streptomycin, bacitracin and neomycin, while the second group contained the mainly bacteriostatic antibiotics aureomycin chloramphenicol and terramycin Members of the first group are sometimes synergistic to each other sometimes indifferent, but never antagonistic. Members of the second group are neither synergistic nor antagonistic to each other but simple additive effects may occur When a member of the second group is added to the first group the combined effect depends on the susceptibility of the organism concerned to the group-one drug when it is susceptible antagonism may occur when it is resistant synergism may be seen. Why synergism occurs remains quite

influenced by the pH of the medium in which it has to act, being most active in alkaline surroundings, but largely ineffective in a neutral or acid medium.

Absorption, distribution and excretion

When given by mouth insignificant amounts are absorbed, and as there is little destruction by the intestinal flora high concentrations are found in the faeces. For most purposes the drug is given intramuscularly although it can be given intravenously subcutaneously or placed directly into cavities. Following intramuscular injection it is readily absorbed at a somewhat slower rate than is penicillin, and a single dose of 0 5 gramme results in detectable blood concentrations for approximately 12 hours.

Streptomycin diffuses widely to most parts of the body In normal subjects only traces reach the cerebrospinal fluid, but in the presence of inflammation significant amounts pass through the meninges. If high concentrations are required, streptomycin must be given directly by lumbar or cisternal puncture.

Following parenteral administration approximately 50–60 per cent of the streptomycin injected is excreted in the urine, and the high levels so reached make streptomycin a powerful urinary disinfectant. In the presence of renal damage the normal route of excretion through the glomeruli is blocked with a resulting rise in the amount of streptomycin in the blood, and in these circumstances there is a risk of producing toxic changes from a dosage which would be safe in patients with normal kidneys.

Toxicity

During the production of streptomycin the parent fungus makes other substances, including histamine, and these contaminants were responsible for some of the toxicity of early samples. Present day streptomycin is almost pure, and undesirable actions are, unfortunately those of the drug itself They consist mainly of damage to the eighth nerve with either disturbance of vestibular function or of deafness. There is some evidence that toxicity is directly related to the blood level and that the maintenance for any length of time of 60 micrograms or more of streptomycin per millilitre of blood is hazardous This level lies at about the upper limit reached by a single dose of 1 gramme, and it is interesting that in the Medical Research Council's trial reported by Bignell, Crofton and Thomas (1951) a dose of 2 grammes a day was followed by giddiness in 60 8 per cent of patients, while a dose of 1 gramme a day produced giddiness in only 16 per cent. Symptomatically there is usually recovery of vestibular function, which may in part be due to compensatory mechanisms. The deafness is permanent.

Dihydrostreptomycin, produced by the catalytic hydrogenation of streptomycin, was at first thought to be less toxic than streptomycin, but experience has not borne this out, since although vertigo is rarely seen, deafness has often occurred, appearing during treatment or even after treatment has finished. In view of the fact that the results of treatment are no better with dihydrostreptomycin than with streptomycin, and that it has this tendency to cause severe and permanent deafness, it has been recommended that this drug should no longer be used (Ormerod, 1952).

Skin reactions occur with all antibiotics, their frequency increasing with the amount of antibiotic used. Streptomycin is no exception, and appears particularly likely to cause contact dermatitis this has been reported in nurses by Strauss

and time-consuming tests are necessary which involve counting the living organisms present in media containing the antibiotics.

Combinations of antibiotics have been used for reasons rather different from those discussed above. In the treatment of tuberculosis with streptomycin the development of resistant strains of tubercle bacilli inevitable if streptomycin is used alone for long enough, can be markedly delayed by the simultaneous use of another effective agent such as *para*-aminosalicylic acid or *iso*-nicotinic acid hydrazide, and such combined therapy is now the rule. How far this is necessary or effective in the treatment of other infections is as yet uncertain.

Penicillin was discovered by the keen observation of a fortunate accident, and the later antibiotics have been due to vast research programmes planned only in so far as they are designed to test practically every product of nature. This hunt has gone hand in hand with investigations of modes of action but despite a decade of work there is still no certain knowledge of the manner in which any of the antibiotics act, and this lack of knowledge constitutes the greatest barrier to a rational approach to the problem of resistance Penicillinase formation constitutes an example, for here, if the way in which penicillin worked and the metabolic pathways through which penicillinase was formed were known, it might be possible to design a drug which although not antibacterial in itself would abolish penicillinase formation and thus render resistant organisms sensitive.

The prospects for rational investigation in the next decade are perhaps better Peters (1952) observes that in the last ten years a great change has come over the subject of intermediary metabolism It seems that at last, even if it be still on the horizon a biochemical geography of the tissue cell can be envisaged in which the enzyme reactions concerned in degrading substances like sugars and fats can be tied to definite histological structures in the cytoplasm" and remote though this may seem from the field of practical medicine, it was the work of Peters and his colleagues at Oxford far from the bedside, that led to the discovery of British anti lewisite so far the only example of a therapeutic agent developed on a logical basis from biochemical principles. A continued expansion of these biochemical investigations coupled with the advances that are taking place in bacterial chemistry may in the next decade lead to the production of antibiotics deliberately designed not only to attack organisms multiplying in the tissue spaces but also to enter the cell and combine selectively with bacteria and viruses lurking there

MODES OF ACTION AND TOXICITY

Streptomycin

The discovery of streptomycin, announced by Schatz, Bugie and Waksman in 1944 was the culmination of years of painstaking research by Waksman and his colleagues. Produced by *Streptomyces griseus* streptomycin in sufficient concentration is a bactericidal drug which is active against many Gram-positive and Gram negative organisms, and particularly against the tubercle bacillus. Fungi rickettsiae and viruses are unaffected Chemically streptomycin is a base, and of the salts which may be formed, the sulphate, hydrochloride and calcium chloride complex are available commercially Solutions of these salts are relatively stable and within a pH range of 6–8 may be kept at room temperature for a month, or in a refrigerator for 3 months with very little loss of activity Streptomycin is

aureomycin, as with terramycin, and to a lesser extent with chloramphenicol, oral administration is followed by a temporary reduction in the number of bacteria in the stools, which frequently become loose and lose their characteristic odour. Doses of 4 grammes or more daily will produce gastro-intestinal symptoms in the majority of patients, but with doses of 250 milligrams at 6-hourly intervals nausea epigastric distress and anorexia should not commonly be seen and may be prevented by giving food or milk before the dose. Aluminium hydroxide gels should not be used as they materially reduce absorption from the gut (Walsbren and Hoeckel, 1950).

Chloramphenicol

The discovery of Chloromycetin was announced by Erhlich, Bartz, Smith, Joslyn and Burkholder in 1947. It is a product of *Streptomyces venezuelae* and is unique in that it is the first antibiotic to be synthesized on a commercial scale. The synthetic drug has the same properties as the natural one: both are known as chloramphenicol, Chloromycetin being the trademark name registered by Parke, Davis & Company. The commercial product is a neutral compound stable in solution, and equally active in acid or alkaline surroundings. It has a bacteriostatic rather than a bactericidal action and possesses a broad spectrum of activity against Gram-positive and Gram-negative organisms and some of the rickettsiae and viruses. The outstanding feature of chloramphenicol is its action on the typhoid bacillus, an organism which is sensitive *in vitro* to a number of agents. Chloramphenicol is so far the only antibiotic which combines effectiveness *in vivo* with ability to cure the disease. Compared with aureomycin and terramycin on a weight for weight basis, chloramphenicol is less active against most bacteria, but this diminished activity is to an extent offset by the higher levels obtainable in the serum.

Absorption, distribution and excretion

Chloramphenicol is rapidly absorbed from the alimentary tract and is excreted mainly through the kidneys. Following single oral doses rather higher concentrations are found in the blood than after similar doses of aureomycin or terramycin, and although the blood level drops more rapidly significant amounts are still present after 6 hours, and some may be detected after 24 hours. Dosage schemes vary but in general for adults a dose of 50 milligrams per kilogram of body-weight per day should be satisfactory; for children the size of the dose should be calculated on the basis of 100 milligrams per kilogram of body-weight per day. The drug should be given 8-hourly to adults and at rather more frequent intervals to infants and children.

The drug penetrates well to all parts of the body and is the only antibiotic which readily enters the normal cerebrospinal fluid, in which concentrations as high as half those of the blood may be found. Some 90 per cent of the drug is excreted in the urine, and although a considerable proportion is in an inactive form, sufficient is left to exert a useful effect in urinary infections.

Toxicity

For some time after the introduction of chloramphenicol few toxic reactions were reported, and the majority of those using the drug commented on the absence

and Waring (1947) Crofton and Foreman (1948) and others, and has occurred during the manufacture of the drug. It may be prevented by wearing rubber gloves when preparing and using streptomycin solutions.

The risk of serious toxic manifestations and the great ease with which bacteria become resistant to streptomycin has led to suggestions that its use should be confined to the treatment of tuberculosis, and possibly of urinary infections.

Aureomycin

Aureomycin is a yellow crystalline substance produced by *Streptomyces aureofaciens* an organism that was isolated in 1948 by Duggar working at the Lederle Laboratories division of the American Cyanamid Company It is primarily a bacteriostatic drug, and in scope is a broad spectrum antibiotic effective against Gram-positive and Gram-negative bacteria as well as some of the rickettsiae and viruses. It has no action on fungi In the absence of moisture aureomycin and its salts are stable, and may be kept for months at room temperature. Acid solutions retain most of their activity in the cold but at 37° after 5 hours 15 per cent of the activity is lost and after 24 hours 50 per cent is lost Neutral and alkaline solutions are unstable. The commercial form usually available is the hydrochloride.

Absorption, distribution and excretion

Aureomycin is rapidly absorbed from the alimentary tract and is usually given by mouth in capsules to disguise the bitter taste. Absorption from the gut proceeds at a constant rate, and within practicable limits cannot be accelerated by increasing the dose. If the dose is increased there is no concomitant rise in the blood concentration, but absorption is continued for a longer time (Brainerd and his colleagues, 1951) Excretion is slow and for the majority of adult patients 250 milligrams at 6-hour intervals will produce and maintain satisfactory serum concentrations with little risk of gastro-intestinal irritation Given intramuscularly absorption is poor and there is considerable pain at the site of injection Intravenous preparations are available for patients who cannot take the drug by mouth This method of administration rarely produces toxic side reactions but is frequently followed by thrombophlebitis. For an adult 500 milligrams given every 12 hours would be an average dose.

Given either orally or intravenously aureomycin diffuses freely throughout the body entering pleural fluid synovial effusions and the bile, in which it is concentrated The majority of authors have detected it in the cerebrospinal fluid, and the results in the treatment of meningitis confirm that at any rate in the presence of inflammation aureomycin passes through the blood brain barrier It is present in high concentration in the urine and following oral dosage can be found in the stools There is some uncertainty as to how far aureomycin penetrates the intact skin, but judging by the results of treatment, it diffuses through it in the presence of inflammation

Toxicity

Aureomycin appears to be free from any serious toxic effect when used in reasonable dosage, although a number of minor reactions may occur and these have sometimes been sufficiently severe to preclude further use of the drug. With

faeces, sometimes with a marked though temporary effect on their consistency and odour High concentrations are present in the urine.

Toxicity

Terramycin is remarkably free from serious toxic effects, those that occur usually being mild gastro-intestinal disturbances associated with loose stools. Sensitivity reactions have been reported, but so far only rarely Whether this represents a fortunate property of the drug or the relatively short time that it has been in use remains to be seen

Bacitracin

Bacitracin was isolated from an organism of the *Bacillus subtilis* group by Johnson, Anker and Meleney in 1945 It is a polypeptide, resembling in this respect polymyxin, which it also resembles in having nephrotoxic properties. At room temperature it is a fairly stable compound, but stability is linked with purity Highly purified preparations approaching the theoretically maximal values of 60 units per milligram rapidly lose potency and in the course of a few days fall to the region of 40 units per milligram at which level they remain. The range of bacitracin compared with those of the broad-spectrum antibiotics is a limited one which includes the Gram-positive cocci and some of the clostridia. It has little action on most Gram-negative organisms, although meningococci, gonococci and *Haemophilus influenzae* are exceptions to this generalization. Fungi are unaffected.

The capacity for causing renal damage, which has been accompanied by albuminuria and a rise in the blood urea, has severely limited the use of bacitracin and it is now employed mainly in the local treatment of infections insensitive to other antibiotics. A further small field which has been only tentatively explored is its use in synergistic combination with another antibiotic in the treatment of resistant infections.

Polymyxin

There are several polymyxins designated A, B, C, D and E, all of which are derived from various strains of *Bacillus polymyxa* a widely distributed soil organism. They are all polypeptides, differing in the number and kind of amino acids present, and they were discovered by three groups of workers within a short space of time. Benedict and Langlykke (1947) reported the antibacterial properties of cultures of *B polymyxa*, and in the same year Ainsworth, Brown and Brownlee (1947) described aerosporin which they isolated from an organism known as *B aerosporus* This was later found to be identical with *B polymyxa*, and it was agreed to call all antibiotics of this group polymyxins. Finally in the same year another polymyxin was reported by Stansly Shepherd and White (1947).

All the polymyxins have been found to cause renal damage, although there is a variation in degree, polymyxins B and E being less toxic than A, D and C. In addition, neurological symptoms including paraesthesia, dizziness and weakness of the limbs have been observed with polymyxin B. These various toxic effects have removed polymyxin from the list of antibiotics which can be used with safety and it is regrettable that this should be so, as it is a bactericidal drug highly active

of such reactions There is little antibacterial action on the intestinal flora, and the loose stools and diarrhoea seen with aureomycin and terramycin seldom occur

Chloramphenicol contains a nitro-benzene radical and the first suggestion that *chloramphenicol might effect blood formation* came from Recinos and his colleagues (1949) who noticed transitory leucopenia while treating children with pneumonia. Since then Gill (1950) and a number of other authors have found that chloramphenicol may lower the white-cell count, but reports have been few and such a depression cannot be regarded as a serious hazard of chloramphenicol therapy A much more serious toxic reaction was first reported by Rich Ritterhof and Hoffman (1950) These authors described a fatal case of aplastic anaemia following almost 3 months treatment with chloramphenicol for a urinary infection and after a lag of a year further cases have been reported At the time of writing so little information is available that an assessment of the likelihood of aplastic anaemia developing as a result of treatment is not possible. According to one authority the risk is probably not less than 1 in 100 000 nor more than 1 in 10 000 courses of treatment (Witts, 1953) but these figures are hard to reconcile with series such as those of Wilson and his colleagues (1952) who described the occurrence of aplastic anaemia in 2 out of 62 patients treated for bronchiectasis There is as yet no clear indication that aplastic anaemia is more likely to follow long courses of treatment rather than short ones, repeated courses rather than single ones, or courses in which some other drug is used in addition, and until these points are known the future value of chloramphenicol will remain uncertain When other antibiotics are available typhoid fever is the only imperative indication for the use of chloramphenicol and for the time being it may be considered advisable to *restrict its use to the treatment of this disease* and to that of infections due to strains of bacteria resistant to other agents. Indiscriminate use, or use for the treatment of trivial conditions, is certainly to be deprecated

Terramycin

Terramycin the latest of the broad spectrum antibiotics, was announced by a team of workers from the Pfizer Company in 1950 A product of *Streptomyces rimosus* it is amphoteric in reaction and is stable in solution The range of antibacterial activity resembles that of aureomycin in that Gram positive and Gram-negative organisms are affected as well as certain rickettsiae and viruses. The closeness of the comparison with aureomycin is probably more than coincidental chemically the two antibiotics appear to be very similar and bacteria found resistant to one are nearly always resistant to the other

Absorption distribution and excretion

Absorption from the alimentary tract is rapid and the drug may be detected in the serum within 30 minutes of its administration The concentration in the blood increases as the oral dose rises from 0 5 gramme to 1 gramme, but above this level little further increase in the blood concentration takes place. Single doses produce satisfactory blood levels for 6 hours, and some terramycin is frequently detectable for 24 hours. If the drug cannot be given by mouth an intravenous preparation is available.

Terramycin diffuses readily through the body passing when inflammation is present into the cerebrospinal fluid A considerable amount is excreted in the

TRENDS IN TREATMENT

Actinomycosis

It is now almost certain that human actinomycosis is due to *Actinomyces israeli*, an organism found only in man. There is no doubt that this organism is distinct from *A. bovis* which is responsible for actinomycosis in cattle, and from *A. graminis* a harmless aerobic saprophyte found on grasses. True examples of *A. israeli* have been recovered from normal mouths, and actinomycosis following a compound fracture of the mandible is presumably due to direct infection. The route by which other sites in the body are infected is unknown.

The outlook for patients suffering from actinomycosis has been entirely altered by penicillin, and providing that the diagnosis is made in time there is now a reasonable hope of cure for every form of the disease. Naturally occurring strains of *A. israeli* resistant to penicillin are very uncommon. Garrod (1952a) stated that of 30 strains examined by him none required more than 0.25 unit per millilitre of penicillin to inhibit growth, and the large majority required less. These figures refer to determinations in which suspensions of the organism were used as an inoculum; if the sensitivity test is carried out using whole colonies for the inoculum, up to 5 times as much penicillin may be required, and this is probably applicable to conditions in the body. In addition, as actinomycosis of any standing is usually accompanied by a considerable amount of fibrosis, sufficient penicillin must be given for a long enough period of time to ensure that there is penetration to the centre of the diseased areas. This necessity for large doses continuing for several weeks may be obviated if the infection is near the surface, and penicillin can be applied locally.

A. israeli may acquire a moderate degree of resistance to penicillin during treatment, and for patients in whom this becomes a problem, a variety of other antibiotics are available. Garrod (1952b) found the mean minimum inhibitory concentrations (expressed as micrograms per millilitre) of the newer antibiotics for 12 strains to be: streptomycin 23.7, aureomycin 4.2, chloramphenicol 2.8, and terramycin 2.2, findings which suggest that with the possible exception of streptomycin, these newer antibiotics should be effective in treatment. Clinical reports of their use are so far rather few, but those that have been published claim excellent results with aureomycin and chloramphenicol, and success in some cases with streptomycin (Wright and Lowen, 1950; McVay, Guthrie and Sprunt, 1951; Littman, Paul and Fusillo, 1952; Torrens and Wood, 1949).

Erythema serpens of Morrant Baker (1873) often called erysipeloid of Rosenbach (1884)

Erysipelothrix rhusiopathiae, the organism responsible for this complaint, may be cultivated from the deep layers of excised pieces of skin or from fluid injected into and aspirated from the lesion, but as the diagnosis is usually evident, these procedures are not normally carried out and there is not a great deal of information as to the sensitivity of *E. rhusiopathiae* to antibiotics. Sneath, Abbott and Cunliffe (1951) tested 7 strains which had been isolated from patients described by Price and Bennett (1951). They found all the strains to be sensitive to penicillin and to aureomycin, chloramphenicol and terramycin; sensitivity to streptomycin varied, some strains being sensitive and others resistant; all were resistant to sulphathiazole and to polymyxin.

against the majority of Gram-negative organisms including *Pseudomonas pyocyanea*. Its parenteral use is now limited to infections in which the risk of toxic symptoms is counterbalanced by the impossibility of using any other antibiotic in their treatment, and to infections such as those of the urinary tract in which the effective dose of polymyxin is less than the toxic dose. Intrathecal administration of polymyxin is apparently free from danger and there have been a number of reports of its efficacy in the treatment of meningitis due to *Ps. pyocyanea*. Absorption from mucous membranes, wounds and the gut is so slight that no harm has come from prolonged local or oral administration, and used in this way polymyxin may be of considerable value. It is claimed that bacterial resistance to polymyxin develops only with difficulty and that skin sensitization is rarely seen, and as the rate of skin sensitization to bacitracin is also low the two antibiotics have been combined in a single ointment, and Gastineau and Florestano (1952) stated that excellent results followed its use in the treatment of superficial skin infections. Their ointment contained polymyxin B sulphate, 8 000 units per gramme, and bacitracin, 400 units per gramme. The base was composed of liquid petrolatum, white petrolatum, a polyhydric alcohol fatty acid ester (glyco wax S932), poly ethylene glycol 400 di-stearate and polyethylene glycol 400 di laurate.

Viomycin

Viomycin, isolated from *Streptomyces puniceus*, was first described by Patelski (1950). The chief attraction was that it was effective *in vitro* against streptomycin-sensitive and streptomycin-resistant strains of the tubercle bacillus although less active than streptomycin against other bacteria. Trials have shown it to be of use in the treatment of experimental tuberculosis in animals, and in the treatment of patients, but while being less effective than streptomycin it is also considerably more toxic, causing renal damage, neurological symptoms and electrolyte imbalance. These toxic effects are sufficiently severe to make it doubtful if there is any future for the systemic use of viomycin. No reports have yet been seen of its use as a local application.

TABLE

SENSITIVITY OF SOME PATHOGENS TO 7 ANTIBIOTICS

Organism	*Average minimum inhibitory concentrations in micrograms per millilitre*						
	Penicillin	*Strepto-mycin*	*Aureo-mycin*	*Chloram-phenicol*	*Terra-mycin*	*Bacitra-cin*	*Poly-myxin*
Staph. pyogenes	0 02R	16	0·5R	16R	1R	2 5	200 +
Strep pyogenes	0 01	50	0·5	3	0 5	0·3	400 +
N gonorrhoeae	0 003	6	0·8	0·8	0·8	6	300
Myco tuberculosis	1,000 +	0 1	—	—	—	—	—
B. anthracis	0 022	1	0·1	3 5	0·1	—	—
E. rhusiopathiae	0 08	12–50	2	7	—	—	80 +
A israeli	0 06	23 7	4 2	2 8	2 2	—	—
Proteus	20R	50	200	25R	200	1,000 +	1,000 +
Ps pyocyanea	1,000 +	50	200	500	200	1,000 +	1

Note R = resistant strains common. All bacteria may become resistant to streptomycin. Some omissions in this Table of organisms of dermatological interest are due to the impracticability of growing the organism *in vitro* (for example *Tr pallidum* and *Myco leprae*), others to the paucity of reports in the literature.

TRENDS IN TREATMENT

Actinomycosis

It is now almost certain that human actinomycosis is due to *Actinomyces israeli* an organism found only in man. There is no doubt that this organism is distinct from *A. bovis* which is responsible for actinomycosis in cattle, and from *A. graminis*, a harmless aerobic saprophyte found on grasses. True examples of *A. israeli* have been recovered from normal mouths, and actinomycosis following a compound fracture of the mandible is presumably due to direct infection. The route by which other sites in the body are infected is unknown.

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lines as treatment for syphilis, and it is now realized that though the skin lesions of primary or secondary yaws can be healed the real cure of yaws can be as difficult as that of syphilis. Infectious relapses are not infrequent after short courses of arsenicals (Pardo-Castello, 1939), and arsenicals are not without toxicity more especially in undernourished subjects. In areas where both yaws and trypanosomiasis are endemic, arsenic resistant trypanosomes may be readily produced, and for these reasons and on account of the expense, the use of arsenic for the treatment of yaws, at least in tropical Africa, is undesirable.

Penicillin provides a more effective agent, and one free from toxicity On grounds of convenience repository forms of penicillin have been found most useful, two injections of 1,200,000 units at intervals of 3–5 days proving satisfactory This might be a most suitable opportunity for the use of N N-dibenzylethylene diamine penicillin described by Elias, Price and Merrion (1951). With this preparation detectable levels of penicillin can be maintained in the blood for 14 days or more, and here at last would seem to be a chance of curing these infections with a single injection.

The newer antibiotics, aureomycin, chloramphenicol and terramycin have all been used with success, and by some authors with more success than penicillin (Loughlin, Joseph and Schaeffer 1951 Loughlin and Joseph, 1951 Payne, Bellerive and Jean, 1951) The fact that these antibiotics can be given by mouth may be advantageous for the individual patient, but is of doubtful value in mass treatment where there is a happy certainty about an injection which is not always present with oral medication, particularly when the patients themselves are responsible for taking the drug.

The possession of satisfactory relatively cheap non-toxic agents has for the first time made possible campaigns for the eradication of non-venereal treponematoses, and such campaigns are in progress in various parts of the world. Ambitious though these schemes may seem, the eradication of sibbens (a malady which somewhat resembled yaws and syphilis) from the Highlands of Scotland during the last century has shown that non-venereal treponematosis can be eliminated It will be most interesting to see if mass treatment alone is effective, without an accompanying improvement in the general conditions of life.

Anthrax

At the present penicillin is undoubtedly the first choice for the treatment of anthrax. Prompt clinical response follows its use, and recovery is the rule Among the larger series of patients treated with penicillin, Ellingson and his colleagues (1946) treated 25 cases, all of whom recovered despite the fact that positive blood cultures were obtained in 3 patients. La Bocetta (1948) treated 36 patients with cutaneous anthrax with excellent results His findings, which agree with other workers, were that the organism had usually disappeared from the lesions within 24–72 hours, and that symptomatic improvement was seen within this time.

The susceptibility of *Bacillus anthracis* to the newer antibiotics has been investigated by a number of workers. Garrod (1952c), in the examination of 18 strains, found them all to be sensitive to penicillin, aureomycin, terramycin, streptomycin and chloramphenicol, and these laboratory results have so far been borne out in practice. Clarke (1952) treated 4 cases with chloramphenicol all of whom

Erysipeloid is a self limiting infection and this has led to some difficulty in assessing the results of treatment. King (1946) reporting the treatment of 115 cases of erysipeloid, found the average duration under treatment to be 17·4 days, but pointed out that there was considerable variation between cases, ranging in his series from a maximum of 51 days to a minimum of 7 days. He found penicillin applied as an ointment to be ineffective, a finding confirmed by Speight (1951) in the observation of over 1 000 cases seen in the course of 7 years. Most authors have found the sulphonamides to be of no value and the antibiotic of choice is penicillin which has a prompt and well marked effect on the course of the disease, although relapses are likely to occur if treatment is stopped while any signs of infection are present

The sensitivity findings suggest that the newer antibiotics should be as useful as penicillin in the treatment of erysipeloid but so far the only evidence in support of this view is the report by Waage (1950) who described "seal finger presumably an infection with *Erysipelothrix* which occurs among Norwegian seal hunters, and responds rapidly to aureomycin

Non-venereal treponematoses

It is now recognized that infections due to the treponemas, closely allied to if not identical with *Treponema pallidum* are widely scattered throughout the world. That to-day they are found more especially in tropical and sub-tropical countries is probably related to the primitive living conditions in these regions, and the greater opportunity for the non-venereal spread of infection Examples of these diseases include yaws, pinta bejel of Iraq and Syria and the infection njovera found in Southern Rhodesia. For all these forms the arsenicals were valuable, but they have now been replaced by penicillin and the later antibiotics.

Bejel and njovera

The value of penicillin in the treatment of bejel has been shown by Akrawi (1949) and Hudson (1951), and in the treatment of njovera by Willcox (1951). In these and allied infections symptomatic improvement is rapid but complete serological reverse is slow even after large doses of penicillin

Pinta

This disease is now endemic in Mexico Venezuela Ecuador Columbia Brazil and throughout Central America and it is estimated that at least 1 million cases exist Penicillin was first used by Zoraya, Varela and Castro Estrada (1944). They found that the treponemas, which had been isolated by Saenz, Grau Triana and Alfonso-Armenteros in 1938 and named *T carateum* disappeared from the lesions in 8 hours, and the excellent clinical response to the treatment of this disease with penicillin has been confirmed by other authors. The newer antibiotics have been employed successfully but in the hands of some workers have not been as valuable as penicillin (Rein, Kitchen Marquez and Varela, 1952)

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recovered and Gold and Bogen (1951) treated 8 cases of cutaneous anthrax in 2 of which aureomycin was used in 4 chloramphenicol and in 2 terramycin. All these patients responded well and it is gratifying that for the treatment of this once malignant disease there is now a selection of reliable antibiotics available.

ACKNOWLEDGMENT

I would like to take this opportunity of acknowledging my indebtedness to Professor L. P Garrod for what he has taught me of chemotherapy He should not of course, necessarily be held responsible for statements in this chapter

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CHAPTER 16

CORTISONE AND ACTH IN DERMATOLOGY

MARION B SULZBERGER
With an Introduction by Bram Rose

INTRODUCTORY REMARKS ON THE GENERAL PROPERTIES AND SIGNIFICANCE OF ACTH AND CORTISONE

THE ANTERIOR PITUITARY secretes ACTH (corticotropin), the chemical nature of which is not clearly known although it is probably a polypeptide. Liberation or administration of ACTH stimulates the cortex of the adrenal gland to hypertrophy and increases secretion of a group of biologically active steroids. These are referred to collectively as corticoids. They are of known chemical structure and may be divided conveniently into three groups according to their major properties. The most important to this discussion are the glucocorticoids with an oxygen on C_{11} (see p 315) Cortisone and hydrocortisone (compounds E and F of Kendall) are the prime examples. It is possible to assay the metabolic end product of the gluco-corticoids in the urine by biological means, and this is probably the most reliable test for activity of this type of compound The second group of corticoids elaborated by the adrenal cortex is androgenic in nature being related to testosterone. The androgenic corticoids are metabolized to the 17 ketosteroids which may also be assayed in the urine. While assay of the urinary 17 ketosteroids is an indication of adrenocortical activity it provides little information regarding the production of 11-oxycorticoids or cortisone like activity A third type of corticoid for which no practical test has as yet been devised is that related to desoxycorticosterone. This has its major effect on electrolyte and water metabolism.

Since the effects of ACTH are mediated through the release of cortisone or hydrocortisone, the effects of administration of both types of compound may be considered together

Carbohydrate metabolism is altered through an increased production of glucose from protein In addition the utilization of carbohydrate is reduced There may therefore be impaired carbohydrate tolerance with hyperglycaemia and glycosuria It is possible that continued administration of these hormones may lead to diabetes mellitus but the incidence is low and seems to occur only in patients with a diabetic background A patient with mild diabetes may be treated for short periods if necessary without fear of permanently increasing the severity of the diabetes Severe diabetes, however is a contra indication to the use of these hormones

Protein metabolism is altered in that a negative nitrogen balance occurs, but this is not often of great clinical significance However if osteoporosis is present it is probable that loss of protein may further aggravate the condition along with the loss of calcium that occurs spontaneous fracture of vertebrae may then occur It is necessary to correct osteoporosis by the administration of a high protein diet

a calcium supplement and testosterone before administration of ACTH or cortisone, and this régime should be maintained as long as these hormones are used.

A tendency for fat depots to be shifted may be seen with prolonged administration or high dosage. This may become manifest by the appearance of moon faces, fat pads or general obesity. These changes appear to be related in part to hereditary factors, being more prone to occur in those with a family background of obesity.

Changes in the electrolyte pattern are inconsistent, with a tendency to sodium and chloride retention. One of the common side effects secondary to this is the production of dependent oedema which can be overcome by the restriction of salt in the diet.

Transient hypertension is more common after the administration of ACTH possibly due to the fact that desoxycorticosterone-like compounds are released from the adrenal glands as well as cortisone. It is seldom seen with oral cortisone therapy. As a general rule, ACTH and cortisone should not be administered to patients with marked hypertension.

Potassium excretion is enhanced by a change in the tubular mechanism of the kidney but the symptoms of muscular weakness or electrocardiographic changes are not common. The administration of potassium chloride in enteric coated capsules will correct the deficiency.

Alterations in the blood morphology following ACTH or cortisone therapy consist of a reduction in the circulating eosinophils and lymphocytes, an increase in the polymorphonuclear neutrophils, and a decrease in the erythrocyte sedimentation rate if the latter was previously elevated.

In addition many immune and inflammatory responses may be interfered with. The exact mechanism whereby these changes are brought about is still obscure although lymphoid tissue tends to be reduced. There is evidence to show that the production of certain types of antibody as well as *gamma*-globulin is depressed. The suppression of fibroplasia and other features of the general mechanism of inflammation in conjunction with those described above make it evident that the signs and symptoms of acute infection, or those of a perforated viscus may be completely masked if the dose of ACTH or cortisone is high. So long as one is aware that these conditions may arise, adequate steps may be taken, such as the administration of suitable antibiotics or surgical intervention (*see* p. 298).

Because secretion of hydrochloric acid into the stomach may be increased, and ulcer formation enhanced, ACTH and cortisone should not be given to patients with a history of peptic ulcer except when such administration is necessary to save a life.

In tuberculosis, acceleration of the disease may occur. These compounds are therefore contra-indicated in active or suspected pulmonary tuberculosis. The one exception to this rule is Addison's disease complicated by pulmonary tuberculosis, where both conditions must be treated. It should be noted that the dose of cortisone required for the control of Addison's disease is in the order of 25–30 milligrams of cortisone per day. This is a much smaller dose than is commonly used for the majority of other conditions such as those about to be described. Old, healed pulmonary tuberculosis however does not contra-indicate the use of ACTH or cortisone, but patients with this defect must be carefully watched.

The interference in physiological relations between pituitary and adrenal caused

by the administration of ACTH and cortisone is of considerable importance. For example, ACTH depresses the activity of the anterior pituitary while stimulating adrenal cortical activity Cortisone and hydrocortisone on the other hand depress the activity of both anterior pituitary and adrenal cortex These relationships are shown in Fig. 49

Normally there is a heightened response on the part of the pituitary adrenal mechanism as a result of acute infection, trauma or major surgery Through nervous pathways mediated *via the hypothalamus, the anterior pituitary secretes* ACTH in greater quantity with subsequent response by the adrenal If ACTH or cortisone is administered this mechanism may fail to respond Deaths have been reported following the withdrawal of a daily oral maintenance dose of as little as 50 milligrams of cortisone before a surgical operation In such cases the *adrenals fail to respond to the demands at the time because of atrophy due to*

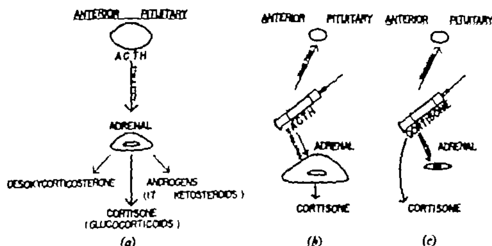


FIG 49 —Relationships and comparisons between the action of adrenocorticotropic hormone (ACTH) and of cortisone. (a) Normal relations (b) Effects of ACTH administration (inhibition of anterior pituitary stimulation of adrenal cortex) *(c) Effects of cortisone (injected or oral). (Inhibition of anterior pituitary and adrenal cortex.)*

hormone therapy Under circumstances such as acute infection or perforation of an abdominal viscus necessitating surgery it is necessary therefore, not only to maintain hormone therapy but *to increase it considerably in order* to avert a state of collapse. For similar reasons, tapering the dose gradually is preferable to abrupt withdrawal when treatment has to be stopped

Finally it is clear that both the desirable, as well as *the undesirable effects of* these compounds are temporary in nature. They neither cure nor do they damage *when properly used.*

THE PRESENT STATUS OF CORTISONE AND ACTH IN DERMATOLOGY

No trend in dermatology is more modern than the use of ACTH and cortisone in no field of medicine have the data accumulated more quickly or in greater mass Much of what one attempts to set down is being altered by new discoveries

at the very moment of the writing and the space allotted to the present section would not suffice for the mere listing of all the pertinent publications. Therefore, in order to obviate a spurious semblance of comprehensiveness or finality it is preferable to state at the outset that the following represents only a few selected topics and that most of the statements made are tentative inferences, not final pronouncements. Those wishing to acquire the most complete and authoritative information at present available regarding the pharmacologic aspects of adrenocortical steroids and ACTH in man are referred to the comprehensive and critical reviews now appearing serially in the *New England Journal of Medicine* (Thorn and his colleagues, 1953 a, b, c and d).

In selecting the topics which follow I have been guided mainly by two considerations (1) my personal acquaintance with the particular subject and (2) my estimate of the value or interest it may have for the clinical investigator or practitioner of dermatology

CONTRA-INDICATIONS AND PRECAUTIONS

It is unorthodox and perhaps also uninspiring to begin by listing dangers, disadvantages and dont's —nevertheless so great are the risks of possible ill effects attending the use of these hormones that I believe it justified to state them at once and as emphatically as possible. It is the conviction of every conscientious physician who has used ACTH and cortisone for any considerable period that these hormones should never be given without the most clear-cut indications, nor for one day longer than necessary nor in a dose one milligram higher than needed. For as Rose has pointed out in his introductory remarks, among the disorders that have been produced or activated are hypertension, congestive heart failure, flare-up and spread of quiescent infections (including tuberculosis), thromboses, haemorrhages, diabetes, perforation of gastro-intestinal ulcers, osteoporosis with spontaneous fractures and psychoses. Add to this list the less dire but decidedly disfiguring disorders such as *acne, hypertrichosis, "moon facies"* buffalo hump striae distensae, obesity and oedema, and it becomes unmistakably clear why therapy with these compounds is usually contra-indicated in mild or non-fatal disorders including mild psoriasis or mild eczematous, contact-type dermatitis or mild atopic dermatitis.

These hormones, however have an important place in modern dermatologic therapy—a position which they will in all probability not only hold but will further

The list of undesirable effects indicates the major relative contra-indications for the use of ACTH or cortisone. Every patient with a present or past disorder in the above list presents a greater risk than do persons who are free from the signs or history of these disorders. Therefore the first step in the prevention of ill effects is careful examination of the patient for hypertension, glycosuria, renal insufficiency occult infections (including if necessary x ray examination for pulmonary tuberculosis), tendency to haemorrhage or thrombosis, gastro-intestinal ulcers and psychic abnormalities and scrupulous history-taking to rule out their previous presence. Should these examinations reveal the presence or history of any of these disorders, the patient must receive the hormones only when the most absolute indications prevail and only under the closest continued medical supervision and the application of all measures required to combat the particular ill effects. Thus

for example the concurrent administration of aureomycin terramycin, and others of the antibiotic group of drugs will be almost routine in those cases showing a tendency or suspected of a tendency to pyogenic infections appropriate diet and perhaps insulin administration will be prescribed in those with disorders of a hyperglycaemic nature.

Even when such disorders are excluded at the first examination it is advisable that every patient receiving the adrenal steroids or ACTH should be committed to the following regimen.

(1) An examination each week or more often, to ascertain blood pressure and weight. It should be noted whether there is any degree of glycosuria whether there is oedema formation and any purpuric effects. Psychic or emotional changes (hypomanic or depressive or agitated) should also be watched for carefully

(2) An examination monthly or oftener should be made noting the blood levels of sodium, potassium and chlorides. When ACTH is given a count for the number of circulating eosinophils should be made.

(3) During the treatment and whenever the physician thinks necessary skeletal x ray examination should be made. Among the other examinations which should be given are tests for urinary 17 ketosteroid and 11-oxysteroid excretion studies of bleeding tendencies and blood-clotting factors fasting blood sugar measurements.

In addition to routine examinations, the following restrictions and supplements are prescribed for all patients on long-term therapy with these hormones.

Routine

(1) A low sodium chloride (salt poor) diet should be enforced to prevent salt and water retention

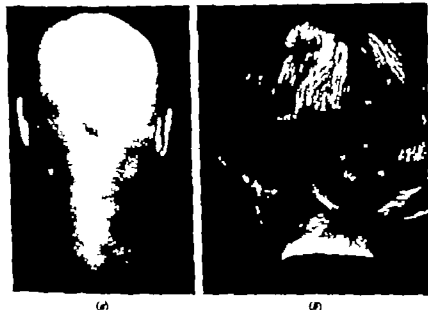
(2) Between 1·0 and 3·0 grammes of potassium chloride should be administered daily in the form of capsules, preferably enteric-coated and taken after meals. This dosage should be adjusted according to the weight of the patient, the amount of cortisone or ACTH the patient is receiving, the clinical findings and symptoms, and the results of the chemical studies of the blood

(3) Other adjuvants as they are required—insulin testosterone calcium and high protein diets antibiotics vitamin C vitamin K Electroshock therapy may be of value in treating psychoses induced by ACTH or cortisone. (A patient suffering from pemphigus who became violently manic under the necessarily huge doses of hormones, promptly returned to his normal psyche after a few electroshock treatments. It is particularly noteworthy that this patient has now for more than 1 year tolerated moderately large maintenance doses of cortisone without untoward psychic or other effects.)

INDICATIONS AND USES

As far as is known today ACTH and cortisone do not cure any disease. When successful they suppress the manifestations and symptoms—their effects may therefore be termed morbidistatic Fortunately it has turned out that this morbidistasis is accomplished without material interference with the natural course of a disease towards its own cure or remission Therefore the administration of these hormones in doses sufficient to suppress the signs and symptoms of

illness amounts to a "cure" if it can be continued until the appearance of Nature's cure. This is easily accomplished in acute, naturally self limited dermatoses such as an acute allergic contact dermatitis from a plant or chemical, or a case of urticaria from a single exposure to a drug or food. Moreover with the precautions described in the preceding section, subacute and chronic skin diseases can often be kept relatively free of signs and symptoms through the long-continued administration of suppressive doses of the hormones. Once again it is most fortunate that the doses required to maintain substantial if not complete relief in many chronic dermatoses are so often within the range of the patient's tolerance. It is now established that many cases of dermatoses such as atopic dermatitis, pemphigus



(a) (b)

FIG. 50 — Woman, aged 40 years (a) Alopecia areata of 34 years duration and alopecia totalis of 3 years duration—before cortisone (b) after 14 months of oral cortisone therapy (Initial dose 200 milligrams per day maintenance dose 75–100 milligrams per day hair again begins to fall out rapidly when dose is lowered to 50 milligrams per day

vulgaris and acute disseminated lupus erythematosus can be maintained on adequately morbidistatic doses of these hormones for over 3 years without serious ill effects To my mind perhaps the most optimistic of all facts in this new field of therapy is the finding that most of our cases which originally required very large doses are now progressively requiring less and less of the hormones (for example, after periods of treatment of 2–3 years, they require only 12 5–100 milligrams of oral cortisone daily as contrasted with original requirements of from 400 to 1,200 milligrams daily (see Fig. 54). Even in pemphigus vulgaris formerly regarded as almost inevitably fatal, a very exceptional patient can be found who is now in remission without requiring any hormonal adjuvants whatsoever and, of course, remission or definitive healing is *finally* often maintained without further hormonal

therapy in chronic but ordinarily self healing dermatoses, such as atopic dermatitis (including infantile eczema) distinctive exudative discoid and lichenoid dermatosis, nummular eczema.

In view of all the foregoing pros and cons, there are few situations in medicine which require more of the physician's judgment and conscience than does the decision whether or not to give cortisone or ACTH in a given case.



FIG 51—Jewish male aged 41 years (a) Typical severe generalized distinctive exudative discoid and lichenoid chronic dermatosis (b) after 6 days on oral cortisone (150 milligrams per day).

In such desperate and ordinarily fatal diseases as pemphigus and acute disseminated lupus erythematosus, the decision is not generally difficult—there is nothing better available today and these hormones should be given as early as possible and in sufficient dosage This will often prolong life and transform a suffering moribund patient into a functioning and relatively happy rehabilitated and useful human being. In chronic and subacute diseases which are never fatal but often highly distressing and incapacitating—severe atopic dermatitis (including infantile

eczema), nummular eczema, distinctive exudative discoid and lichenoid dermatosis of Sulzberger and Garbe, severe acute or chronic contact dermatitis, or severe, total alopecia areata—"to use or not to use" is often as delicate and difficult a decision as any which can cause a modern "doctor's dilemma" For while these diseases do not end life they often ruin it (Rothman, 1952) (Figs. 50–53). It is therefore my opinion that when other known measures have failed and



FIG. 52.—(a) Atopic dermatitis. (b) after one week of oral cortisone.

when the dermatosis is a severe one, when it materially and persistently interferes with all the functions and pleasures which make life worth while, and when the examinations and precautions listed above can be faithfully followed, the carefully controlled use of these hormones is justified. For in so-called "benign dermatoses" also they will often prove to be the touchstone which transmutes a useless and despairing sufferer into a happy useful member of society

There are only two other restrictions which I would place upon this decision to administer cortisone or ACTH The first is that these hormones generally should not be used as the sole measure *but in combination* with all the other modalities

previously found useful in the treatment of the particular type of skin disease for example, local treatment and radiation therapy It is my conviction that one of the very greatest benefits to be derived from cortisone and ACTH in dermatology is that they often rapidly transform a weeping and inflamed constantly scratched and denuded highly irritable and universally intolerant skin surface to which no local remedy can effectively be applied into one which will tolerate and be benefited by external applications of properly chosen topical medicaments. Secondly is that the patient s dermatosis should first have been accurately classified by a qualified physician as indubitably belonging to the class of skin diseases



(*a*) (*b*)

FIG 53 —(*a*) Pemphigus vulgaris (*b*) after 2 months of oral cortisone

known to be favourably influenced by permissible doses of the hormones in question

Those dermatoses which are now considered to be in the category of those which can be helped by these hormones are listed in Tables I and II These Tables are based on the reports of numerous investigators, as well as on my own experience (Baehr and Soffer 1950 Bayles, Stout, Stillman and Lever 1950 Brunsting, 1953 Cannon and his colleagues, 1951 Costello 1951 Dillaha and Rothman, 1952 Ereaux, 1953 Ferriman and Wilson 1950 Frazier and his colleagues, 1951 Grace and Combes, 1949 Haserick Corcoran and Dustan 1951 Kanee, Grant Mallek and Eden, 1950 Kierland and Hines, 1951 Kierland and his colleagues 1952 Roche and his colleagues 1951 Schupbach and Gendel 1951 Siltzbach Posner and Medine, 1951 Sulzberger and his colleagues, 1951 Sulzberger Witten and Yaffe, 1951 Sulzberger and Wolf 1952 Thorn and his colleagues, 1953 Tulipan, 1950)

TABLE I

Dermatoses in which ACTH and Cortisone are Frequently Effective as Morbidistatic Agents

Atopic dermatitis (in the infant, child, adolescent and adult)
Allergic eczematous contact-type dermatitis
Exfoliative erythrodermas (due to various causes, including psoriasis)
Acute and subacute disseminated lupus erythematosus
Pemphigus vulgaris foliaceus vegetans erythematosus
Acute urticaria and angioneurotic oedema
Multiforme erythemas
Nummular eczema
Eczematous eruptions of the hands
Distinctive exudative discoid and lichenoid chronic dermatosis (*Sulzberger and Garbe*)
Impetigo herpetiformis

Based on reports of others

TABLE II

Dermatoses in which ACTH and Cortisone Therapy is Sometimes Beneficial

Cutaneous lesions of chronic lymphatic leukaemia of lymphomas of mycosis fungoides
Sarcoidosis
Pruritus of unknown cause (including pruritus ani et vulvae)
Seborrhoeic dermatitis
Post-herpetic neuralgias
Circumscribed lichen simplex
Chronic discoid lupus erythematosus
Alopecia areata
Scleroderma, sclerodactylia, acrosclerosis
Dermatomyositis
Periarteritis nodosa
Chronic urticaria
† Psoriasis (acute arthropathic pustular erythrodermic)
* Beryllium granuloma
Thrombocytopenic purpura, other purpuras
Lepra reaction

* Based on reports of others
† [illegible] thickened, [illegible] psoriasis vulgaris also yields, but generally only temporarily and only to prohibitively high doses

Although it may be unnecessary I repeat that patients with the non-fatal conditions listed in these Tables *must not all be treated immediately or exclusively* with the hormones. Among the "benign" dermatoses only the most carefully selected severe and incapacitating cases which have *failed to yield* to all other less risky measures are proper candidates for cortisone and ACTH therapy. And even in these, the hormonal treatment is to be added to the other standard approaches, never substituted for them.

DOSAGE AND ROUTES OF ADMINISTRATION

Administration of adrenocorticotropin

ACTH can be given intravenously or intramuscularly For the deep intramuscular route both the ordinary aqueous suspensions and newer preparations which form a depot and permit slow absorption are now available. In all cases the ACTH acts indirectly and therefore only when there is a responsive adrenal cortex which the anterior pituitory hormone can stimulate to produce those steroids which presumably act directly upon the diseased tissues.

In contrast, cortisone (or perhaps other cortical steroid derivates of this hormone, for example, hydrocortisone) acts directly upon the affected tissue.

There are therefore fundamental qualitative differences in the mechanisms of action of systemically administered ACTH and cortisone or hydrocortisone. However in dermatologic practice their therapeutic effects are generally similar or identical The exceptions are those rare instances in which there is insufficient adrenal cortex to respond to the ACTH (for example, Addison's disease) or where there is an allergic reaction to the ACTH—or perhaps even to cortisone. But on a quantitative basis the biologic effectiveness of the different hormones, *different preparations and routes of administration* are by no means equivalent—that is to say 1 milligram or 1 international unit of ACTH given intravenously has biologic effects quantitatively different from 1 milligram, or 1 unit given intramuscularly and in turn these both exert effects different from those of 1 milligram of cortisone given by intramuscular injection or by mouth

TABLE III

COMPARISON OF DOSES OF ACTH AND CORTISONE ESTIMATED TO BE THERAPEUTICALLY OF APPROXIMATELY EQUAL EFFICACY

	ACTH by slow intravenous drip	*ACTH intramuscularly in absorption-delaying vehicle (e.g. gel)*	*ACTH intramuscularly in aqueous solution*	*Cortisone by mouth or by intramuscular injection*
Approximate therapeutic equivalents in milligrams as established in various dermatoses	milligram 1†	milligram [illegible]	milligram 5–10	milligram 10-40
Average initial suppressive dose based on the above approximate therapeutic equivalents	30	60	150	300
Average maintenance dose based on the above approximate therapeutic equivalents	10	20	50	100

Cortisone esters are now obtainable for intravenous administration. At the time of writing the information as to relative biologic effectiveness was not available to the author

† One milligram equals 1 international unit

The approximate effective ratios which have been found to prevail in the therapy of most dermatoses are shown in Table III which is based on an earlier publication (Sulzberger 1952) and on studies by Bloom, Sobel and Pelzig (1953).

Under particular circumstances it may be advantageous to give one hormone or one preparation in preference to the others. For example, in order to get a rapidly progressive pemphigus or acute disseminated lupus erythematosus speedily under control, the physician may choose to give intravenous ACTH by slow infusion. This is usually administered like other drugs by the slow drip method. Ten to 25 to 50 milligrams well mixed in 1,000 millilitres of a 5 per cent solution of glucose in sterile distilled water are administered intravenously during a period of 6–12 hours. It has been found that sometimes it is necessary to give as much as 100 milligrams in each 24 hours in order to get a case of pemphigus under control. As will be seen from Table III this may be regarded as the equivalent of as much as 1,250–4,000 milligrams of oral cortisone—a huge dose. In most dermatoses ACTH by any route will be used only for a period of a few days to a few weeks, and the patient will be switched to an ambulatory state and to oral cortisone as soon as feasible. The exceptions are those rare cases which do not tolerate or are resistant to cortisone by mouth or which require continuing hospitalization or patients who for any reason cannot be trusted to take the oral medication as directed and to come to the physician for the essential regular examinations. In the last mentioned circumstances, slow-acting ACTH gel given by intramuscular injection, or cortisone by the intramuscular route, may be continued in preference to oral cortisone. Another situation requiring ACTH may be a threatened or actual exhaustion of the adrenal cortex by long-continued exposure to large doses of cortisone. While theoretically possible, this must today be regarded as one of the rarest of all the known cortisone ill-effects in man. There are nevertheless some investigators who hold that long courses of cortisone should be interrupted at regular intervals, and short courses of ACTH interspersed in order to bring the patient's adrenal cortex back to normal in size and function. While the adrenal cortex is likely to be reduced both in size and function after long-continued massive administration of cortisone the present consensus is that a rest period of about one week followed by a few injections of ACTH will quite regularly restore both its structure and performance.

Administration of cortisone

All of the above uses of ACTH are the exception rather than the rule in dermatologic therapy. For this reason the following discussion of dosage requirements will be devoted solely to the now preponderant form of dermatologic, systemic therapy with these hormones—namely the oral administration of cortisone acetate. Those wishing to translate these oral cortisone doses into any form of ACTH dosage can be guided by the usual ratios of effectiveness as set down in Table III. With the exception of very severe inveterate cases of common dermatoses and of patients critically ill with the so-called fatal dermatoses (pemphigus, acute disseminated lupus erythematosus) the majority of adult dermatologic patients will require initial doses of between 100–300 milligrams of oral cortisone per day in order to bring their disease under satisfactory control. These are the initial doses generally required, for instance in atopic dermatitis. The doses of these hormones required to suppress a disease in infants and small children may perhaps be slightly smaller

than those required in adults with the same disease (the initial dose may vary from 50 to 150 milligrams) But they are by no means as small as one might expect in considering the infant s and child s lesser weight and size that is the ratio between the infant s or child s maintenance dose and the adult s maintenance dose cannot be calculated on the basis of their relative weights.

In severely or critically ill patients with pemphigus, acute disseminated lupus erythematosus, daily initial doses as high as 1 000–1,500 milligrams of cortisone may be required. But in every type of case, be it benign or dangerous, self limited or chronic, as soon as a satisfactory morbidistatic effect is apparent the initial dose should be lowered by decrements of from 25 milligrams to 50 milligrams or more

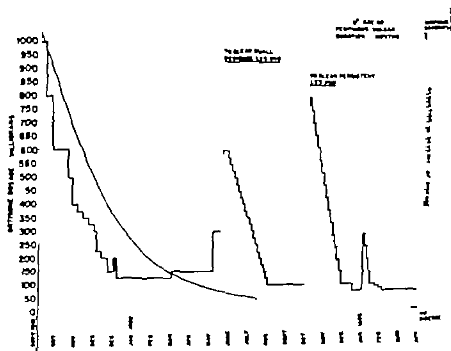


FIG 54 —A typical graph showing decreasing cortisone dosage and concomitant decreasing severity of clinical disease (the latter estimated from the descriptions of signs and symptoms as recorded on the patient s chart) Note the high "Initial dosage" the trend toward ever-lower Maintenance dosage" and the interspersed spikes of higher "Emergency dosage

every few days. This is done until that minimum dose is reached which just suffices to keep the disease under satisfactory control *This dose is then maintained as* long as necessary and so long as it is tolerated but not without continually trying *to go ever lower and lower* *Therefore the physician should in every case make* regular periodic trials at reduction of dosage, and remain on the lowest dosage level achieved unless prohibitive flare ups of the disease occur As stated the most optimistic aspect of this form of therapy is that many of our patients who have now received cortisone continuously for 2–3 years, at present require either a fifth or less of their original minimum dose (Fig. 54)

Although the dosage trend in almost all our cases has been consistently down wards, nevertheless *there have commonly been recrudescences* and exacerbations of the disease which have required a material increase in dosage to establish control

again. However these requirements for elevation of dose have almost all been transient and after a relatively short while it has usually been possible again to reduce the dose and proceed with further gradual systematic reductions.

It will be seen that dosage schedules of these hormones are in all cases flexible affairs which must be continually regulated and quite delicately adjusted to each patient's requirements of the moment. In general however the dosage schedule falls into three natural phases, as follows

Phase 1 *Initial dosage*—This is usually the highest dose required in chronic disease and is to establish control. In acute self-limited diseases such as plant dermatitis or penicillin reactions, the therapy is often limited to this first phase since the disease usually runs its course and terminates in cure during this phase of treatment.

Phase 2 *maintenance dosage*—In chronic dermatoses, this dose is consistently pressed down to the lowest possible level which affords satisfactory relief The maintenance dosage schedule usually represents a descending series of numbers with zero as the limit (*see* Fig. 54).

Phase 3 *emergency dosage*—This consists of temporary elevations of dosage to meet the acute exacerbations and temporary flare-ups and stresses during the course of a chronic dermatosis.

LOCAL EXTERNAL THERAPY WITH CORTISONE AND HYDROCORTISONE

It has already been sufficiently stressed that the systemic administration—and particularly the *prolonged* systemic administration of ACTH and cortisone—may constitute a "clear and present danger" to the patient. I have sometimes expressed it as follows to patients with itching dermatoses who were reluctant to reduce their intake of the hormones You may sleep better while you are taking this dose of hormone but I don't sleep as well Under these circumstances it was natural that physicians should strive to circumvent the dangers of systemic administration by trying to develop local therapy by means of external applications directly to the affected skin.

It was obviously illogical to expect that ACTH would be effective locally since it was recognized that this anterior pituitary principle could not act directly but only through stimulating the adrenal cortex. The first hopes were therefore pinned upon the local application of cortisone to the skin. Despite some early favourable reports, the local application of cortisone proved to be ineffective except under unusual circumstances or in particular sites. Thus some beneficial effects could be noted in certain cases of eczematous and itching dermatoses of the eyelids, and at the junctions of mucous membranes and skin, for example, lips, nares, vulva-anal-perivulva and perianal areas.

The general ineffectiveness of local applications of cortisone to the very skin lesions which yield to the systemic administration of the hormone is still an unexplained mystery However it may be that cortisone is not the active, locally effective principle concerned in benefiting these skin lesions and that the active agent is some derivate or derivates manufactured from the systemically administered cortisone at some internal site [I shall later discuss one strong argument which supports this hypothesis, namely the effectiveness of hydrocortisone (com-

than those required in adults with the same disease (the initial dose may vary from 50 to 150 milligrams). But they are by no means as small as one might expect in considering the infant's and child's lesser weight and size; that is the ratio between the infant's or child's maintenance dose and the adult's maintenance dose cannot be calculated on the basis of their relative weights.

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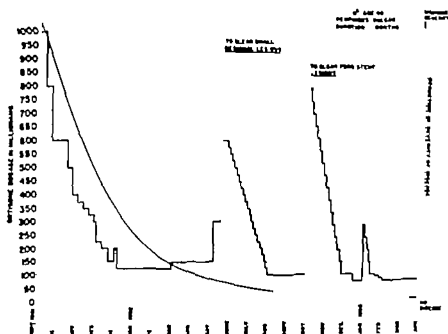


FIG. 54.—A typical graph showing decreasing cortisone dosage and concomitant decreasing severity of clinical disease (the latter estimated from the descriptions of signs and symptoms as recorded on the patient's chart). Note the high "Initial dosage," the trend toward ever lower "Maintenance dosage," and the interspersed spikes of higher "Emergency dosage."

every few days. This is done until that minimum dose is reached which just suffices to keep the disease under satisfactory control. This dose is then maintained as long as necessary and so long as it is tolerated but not without continually trying to go ever lower and lower. Therefore the physician should in every case make regular periodic trials at reduction of dosage, and remain on the lowest dosage level achieved unless prohibitive flare-ups of the disease occur. As stated, the most optimistic aspect of this form of therapy is that many of our patients who have now received cortisone continuously for 2–3 years, at present require either a fifth or less of their original minimum dose (Fig. 54).

Although the dosage trend in almost all our cases has been consistently downwards, nevertheless there have commonly been recrudescences and exacerbations of the disease which have required a material increase in dosage to establish control

messy topical remedy than most agents now in use. The minor unpleasantness and difficulties of external application are certainly insignificant when weighed against the great risks attendant to the systemic administration.

My associates and I have found that concentrations of 1 per cent hydrocortisone in common ointment vehicles are often effective but that some cases do decidedly better when the concentration is increased to 2.5 per cent or even 5 per cent.

Employing these concentrations and with liberal inunctions 2–3 times daily we have achieved beneficial and morbidistatic effects in the majority of cases of the astoundingly wide variety of acute and chronic dermatoses set forth in Table IV while in the dermatoses listed in Table V our results have to date been generally disappointing.

TABLE IV

Dermatoses in which Topical Applications of Hydro-cortisone Hold Promise as a Morbidistatic Measure

Atopic dermatitis (including infantile eczemas)
Contact-type allergic eczematous dermatitis (including dermatitis from plants, occupational substances, etc.)
Otitis externa, i.e. eczema of the ear canal (perhaps combined with antibacterial agents)
Nummular eczema
Seborrheic dermatitis (especially the eczematized and intertriginous forms—e.g. behind ears, under breasts, intergluteal)
Pruritus ani et vulvae
Exfoliative erythrodermas of eczematous or seborrheic type
Eczematous eruptions of the hands and feet (some cases)
Eczematous, patchy and lichenified eruptions of the eyelids, neck, face, etc. as seen particularly in older women
Eczematous and lichenified eruptions of the scrotum, penis, vulva
Distinctive exudative, discoid and lichenoid dermatoses (*Sulzberger and Garbe*)

TABLE V

Dermatoses in which Topical Applications of Hydro-cortisone Have Not Shown Particular Promise

Pemphigus vulgaris
Lichen planus
Alopecia areata
Psoriasis
Discoid lupus erythematosus

It is, I believe, most noteworthy that in a clinical experience which now encompasses several hundred cases, there has not yet appeared a single instance of allergic sensitivity or of intolerance to the local applications of hydrocortisone.

In view of this promising record for safety and of its excellent therapeutic index in so many forms of common dermatoses, its lack of messiness, of the "sting, stink and stain" which so often characterize topical medicaments, I feel that hydrocortisone shows promise of becoming one of the most useful external agents ever developed for dermatologic therapy. Of course the test of time is still lacking

pound F) on local application to the skin lesion These dermatologic observations on the contrasting local effects of cortisone and hydrocortisone are in consonance with the observed ineffectiveness of local injections of cortisone in arthritic joints, as contrasted with the effectiveness of locally injected hydrocortisone.] Moreover there is good evidence from perfusion and other experiments that not cortisone but hydrocortisone is the principal hormone secreted by the adrenal cortex All these facts speak in favour of the hypothesis that not cortisone itself but hydrocortisone and this or other derived steroids are the factors which influence locally the skin lesions and the disabled joints when cortisone is administered systemically Nevertheless this attractive hypothesis is weakened by the established effectiveness of cortisone itself when applied locally in the eye, or nose and on other mucous membranes, as well as the above-mentioned degree of effectiveness of local cortisone at certain sites of juncture between skin and mucous membranes. One of the possible assumptions which would reconcile most of the present contradictions is the idea that certain human mucous membranes are capable of converting the locally applied cortisone sufficiently rapidly into hydrocortisone while such a conversion either could not occur or could not go forward with sufficient speed in the human skin.

But this and the several possible alternative assumptions are still entirely without experimental proof At present they fail to give us any satisfactory explanations, and merely indicate directions for future exploration Regardless of what explanations the future may bring, I believe that it can now be regarded as established that in sharp contrast to cortisone the topical application of hydrocortisone is effective in inhibiting many dermatologic lesions (Goldman, 1952 Goldman and his colleagues, 1952) This statement is made in full recognition of the fact that the topical use of hydrocortisone has been but very recently introduced and that there are only a few publications on its clinical usefulness in dermatologic management (Sulzberger and Witten, 1952 Sulzberger Witten and Smith, 1953). The present findings are therefore subject to revision in the light of further experience.

Our experience to date indicates that in many but not all of the dermatoses responding favourably to permissible doses of cortisone on systemic administration the external application of ointments containing hydrocortisone (either its acetate or the alcohol itself) will if adequately applied bring about substantial *morbidistatic effects* This finding carries with it the usual advantages and disadvantages of topical as against internal medication The principal advantage (and it is here a very great one indeed) is that the absorption of the topically applied agent is apparently negligible, and as far as we know today no systemic ill effects are to be feared even from long-continued use and inunction over extensive areas of damaged skin This statement is supported first by our clinical experience of over 1 year on several hundred patients without a single instance of observable systemic effects from the local application and second, by experimental evidence of lack of systemic effect on inunction of large amounts (Smith, 1953). The drawbacks of topical application include the obvious ones of the messiness and arduousness of smearing on an ointment or applying some other form of topical remedy several times daily as contrasted with the cleaner easier way of swallowing a few tablets or holding the buttock still for an injection However the material itself is colourless and odourless and can be incorporated in the most pleasant types of creams or other vehicles so that it is a much less

messy topical remedy than most agents now in use. The minor unpleasantness and difficulties of external application are certainly insignificant when weighed against the great risks attendant to the systemic administration.

My associates and I have found that concentrations of 1 per cent hydrocortisone in common ointment vehicles are often effective but that some cases do decidedly better when the concentration is increased to 2.5 per cent or even 5 per cent.

Employing these concentrations and with liberal inunctions 2–3 times daily we have achieved beneficial and morbidistatic effects in the majority of cases of the astoundingly wide variety of acute and chronic dermatoses set forth in Table IV while in the dermatoses listed in Table V our results have to date been generally disappointing.

TABLE IV

DERMATOSES IN WHICH TOPICAL APPLICATIONS OF HYDRO-CORTISONE HOLD PROMISE AS A MORBIDISTATIC MEASURE

Atopic dermatitis (including infantile eczema)
Contact-type allergic eczematous dermatitis (including dermatitis from plants, occupational substances, etc.)
Otitis externa, i.e., eczema of the ear canal (perhaps combined with antibacterial agents)
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and much still remains to be studied and learned At present we believe that the usefulness of local hydrocortisone may extend to certain very common forms of skin damage not listed in Table IV Moreover it is my impression that topical use can advantageously be combined with internal administration of cortisone or hydrocortisone It appears to me that the administrations are often complementary in their effects and greater good can be achieved with smaller internal doses and therefore less risk

There still remain many fundamental theoretical problems as well as practical questions to be answered in regard to this very new form of topical therapy *Among the theoretical problems are those relating to the sites and mechanisms* of action upon the skin Perhaps these will be brought nearer to solution by the application to the skin of the radioactively tagged cortisone and hydrocortisone now becoming available to investigators.

Among the practical problems are of course the questions as to just how valuable the local applications will prove to be in the prevention and treatment of occupational dermatoses, skin diseases in military personnel eruptions due to flowers and plants, to cosmetics, dyes and medicaments Will regular external application of an effective morbidistatic measure such as hydrocortisone succeed in reducing the tremendous morbidity and disability from such pandemic skin diseases?

Another group of questions awaiting exploration are those dealing with the possible combination of local hydrocortisone with other time-tested and effective topical dermatologic remedies—tars, chrysarobin mercury resorcin sulphur antibiotics. For instance will the incorporation of hydrocortisone with these local remedies reduce the incidence of medicamentous sensitization and irritation and thus improve the local treatment of eczematous dermatitis, or psoriasis, or acne, or pyodermas, or seborrhoeic dermatitis?

Perhaps even more important than the preceding question is the practical one of what will happen when millions of persons have employed local applications of hydrocortisone over a period of years. Will sensitization or late ill effects occur? *(As stated above, thus far during a period of over a year and among* several hundred users, none has appeared) Will the effectiveness of the hormone diminish with continuing local applications? Or will the same propitious situation develop as with the systemic administration? *That is, will it be the rule that the skin* disease is gradually brought under better and better control so that the doses required to maintain morbidistasis gradually get less and less? At any rate, at present there is no reason to assume that the progressive improvement seen in many cases of chronic dermatoses while under systemic hormonal treatment will not occur also with the use of topical applications.

MECHANISMS OF ACTION PHYSIOLOGIC AND IMMUNOLOGIC EFFECTS

The regular often dramatic improvement which ACTH and cortisone can achieve in so many different dermatoses is undoubtedly due to some fundamental non-specific influences upon certain common denominators which are basic to the different aetiologic constellations. Nevertheless none of the physiologic or immunologic mechanisms of action known today suffices to explain fully the consistent and tremendous effects of the hormones upon inflamed areas, oedema

itching and like responses. However the combination of known effects, and others not yet elucidated, seem to work together to suppress the local tissue reactions, to inhibit or arrest the disease manifestations which result from a great variety of different forms of local "stress"

TABLE VI

Some of the Important General "Physiologic Effects" of ACTH and Cortisone

Systemic

Increased retention of sodium and water
Increased urinary excretion of potassium and chlorides
Increased carbohydrate metabolism (with increased glyconeogenesis and increased excretion of glucose (lowered renal threshold))
17-Ketosteroid excretion (decreased with cortisone (?) increased with ACTH)
11-Oxysteroid excretion (increased with both)
Increased absorption and storage of lipids (increased cholesterol blood levels)
Increased protein katabolism

Psychoneurologic

Increased nervous and psychic lability (insomnia, euphoria, depressions manic, and other psychoses)

Haematologic and Cytologic and Biochemical

Reduction in number of circulating eosinophils
Reduction in number of circulating lymphocytes
Inhibition of fibroblastic activity in tissues (diminished fibroplasia)
Diminished formation of granulation tissue
Diminished hyaluronidase activity in tissues

TABLE VII

Effects upon Skin Functions and Reactions by Systemic Administration of ACTH or Cortisone in Sufficient Amounts

1 Reduction of the quantity of ether-soluble material (essentially sebum) delivered to the skin surface
2 Increase of the amount of sweat delivered upon thermal stimulation
3 Reduction of the concentrations of sodium and of chlorides in the excreted sweat
4 Increase of the temperature of the skin surface
5 Increase of the rate of blood flow in the minute vessels as observed with the capillary microscope as well as in near ultra-violet rays after intravenous injection of fluorescein
6 Acceleration of the disappearance of the wheals produced by physiologic saline solution in the McClure-Aldrich test (probably due to the effect of retention of sodium chloride in the skin, and accelerated peripheral vascular flow)

Immunologic Responses

7 Reduction of the tuberculin-type responses (results quite inconsistent in man)
8 Reduction of the patch test responses (but not to such degree as to interfere materially with the eczematous reactions to diagnostic patch tests applied in the usual manner with standard concentrations of allergens)
9 Little if any influence upon the urticarial response to intracutaneous injections or the passive sensitization of the skin by Prausnitz-Kuestner passive transfer antibodies

Among the known general physiologic" effects are those listed in Table VI In considering the mechanisms of the hormonal effects upon the skin diseases, one must add to these general effects the more particular influences upon the skin and skin reactions. Studies of these cutaneous phenomena are still sparse the list in Table VII is not definitive but consists of inferences gleaned from a very small series of recent investigations. (Leith, Graham and Burrage, 1951 Sulzberger and his colleagues, 1951 *Schweizerische Academie der Medezinische Wissenschaften*, 1952 Appel Fulton and Orr 1952 Nilzen 1952 Sacks, 1952 Rose and his colleagues, 1951 Sulzberger Witten and Zimmerman 1952 Thorn and his colleagues, 1953 b c and d)

WHAT OF THE FUTURE?

In many respects medicine is still on what may be called a "shakedown cruise as regards the clinical uses of these hormones, and what their full combat performance will be in the fight against disease remains unknown However it is certain that medicine has already gained a tremendously increased understanding of how the organism and the tissues resist a very great variety of stresses, ranging from infections to physical and emotional onslaughts (Selye, 1950 Thorn and his colleagues, 1953 a, b c and d)

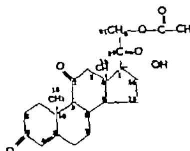
Many of the clinical problems are clear—they lie not only in the direction of finding additional uses for the new hormones, but mainly in seeking to modify these hormones, to explore the possible uses of their chemical relatives, to vary their routes of administration and vehicles and in general to discover new procedures which will increase both their safety and effectiveness Some of these directions for clinical progress have already been mentioned in the discussion of the future potentialities of external applications of hydrocortisone acetate. Another promising field has just begun to be explored—that is the use of cortisone or ACTH in conjunction or alternation with other systemic remedies, for example, with bismuth or atabrine (mepacrine) in all forms of lupus erythematosus with sulphones in the treatment of leprosy with the indicated antibiotics in treating various infections with other hormones (insulin, thyroid, testosterone) in treating endocrine disorders. The inestimable advantages residing in the combined use of *systemic* administration of the hormones and *external* treatment of the skin lesions have already been emphasized

In addition to mentioning such clear-cut opportunities for clinical progress, it is safe to predict that there is scarcely a fundamental field of basic dermatologic investigation which will not be enriched and enlarged by the use of these hormones.

Not the least among the many fascinating prospects for dermatologic research are the new opportunities for studying in a much more precise and objective manner just how certain non specific measures such as autohaemotherapy (Sauer 1951) fever therapy "foreign protein therapy shock treatments, surgical intervention, and many other tried but mysterious measures all suppress or relieve the manifestations of unrelated diseases

To my mind one of the most important of the new opportunities lies in the fact that the study of the effects of cortical steroids upon skin lesions may bring with it a more rational and scientific approach to the problems of how the mind and

emotions stimulate or inhibit certain somatic changes. For it is certainly conceivable that such common mysteries as the cures of warts and mollusca contagiosa by suggestion and hypnosis, and the occurrences and recurrences of herpes simplex and alopecia areata under emotional upsets may depend upon the corticocortical axis—that is, what is today vaguely described as psychosomatic effects may have some quite intimate connexion with the ways in which the cerebral cortex can influence the adrenal cortex in its production and liberation of cortical steroids.



The structural formula of cortisone acetate (11-dehydro-17-hydro[illegible]-21-acetate) showing the method of numbering the carbon ring structure.

In view of the tremendous impact which these hormones have exerted upon dermatologic investigation during the 4 brief years since their introduction to medicine, it is not at all venturesome to predict that in the future they may well prove even more useful in dermatologic research than in dermatologic therapy for these hormones and their effects are clearly and intimately concerned with the most basic and "biologic" of all the functions of the skin—namely its physiologic function to protect the individual against the multitudinous onslaughts of his environment and the inevitable stresses which form the very pattern of life.

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CHAPTER 17

BETA-RAY THERAPY

I G WILLIAMS

HISTORICAL INTRODUCTION

BETA-RAY plaques using radium salt as a source have been in use in radiotherapeutics for dermatological conditions for many years. Small flat boxes of up to 10 square centimetres and consisting of radium covered with a thin window of

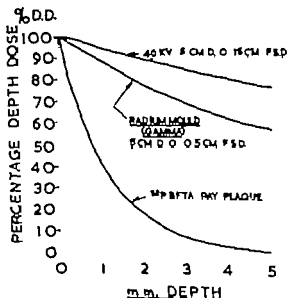


FIG. 55.—Comparative depth-dose curves for low-voltage x-rays, a radium mould and P_{32} plaque.

silver (0·2 millimetre) or 0·1 millimetre of monel metal were employed, the radium content being expressed in milligrams. Treatment was largely empirical and based on experience, as there was no method of measuring dose rates or depth doses. The greater accuracy of low voltage x rays lead to the gradual abandonment of these plaques in therapy but *beta*-ray therapy has definite advantages over low voltage x-ray therapy. At 2 millimetres the depth dose is some 15 per cent, with x rays generated at 45 kV (1 millimetre Al filter) it is about 85 per cent. With beta rays there are thus no systemic effects, and local effects are superficial so that scarring is very slight epilation will occur but as the hair roots are not destroyed the hair will regrow. It has been stated that this hair is coarser as the finer more

shallow rooted hair may be permanently depilated The emission from radium has a 4 per cent *gamma*-ray contribution, so that the discovery of pure *beta*-ray emitters and recent advances in physics with accurate dose-rate measurements has reawakened interest in this form of radiation therapy (Fig. 55).

The first use of radioactivity in tracer studies was carried out by Hevesy who, in 1923, published studies of the absorption and excretion of bismuth labelled with its radioactive isotope radium E. He had already devised a method of determining the amount of known and unknown isotopes in a mixture, as well as discovering the phenomenon of diffusion of isotopes in the solid state by Brownian movement, for which he was awarded the Nobel Prize. He extended his work to investigate the uptake of lead in malignant tissue, and disproved the so-called selective uptake of lead in tumours. Artificial radioactivity was discovered by Joliot and Curie in 1934 Since that time extensive use has been made in investigation of physiological and pathological processes by physical as compared with chemical means, and in the treatment of diseases, by the radiation from the disintegration of isotopes.

PRODUCTION OF ISOTOPES

Although isotopes can be produced in a cyclotron by bombarding a target with deutrons or protons, as well as in a linear accelerator most of the ones used in medicine are produced by bombardment of the appropriate target material with neutrons in a nuclear reactor (or pile) The target material is placed in an aluminium can if a solid or in a silica ampoule if a liquid, and positioned in the pile. The apparatus runs for about 140 hours a week, and the irradiation of a target may take up to 4 weeks. By chemical synthesis, organic and inorganic compounds can be "labelled" with radio-isotopes, for example, labelled carbon can be built into an organic compound and physical methods used for physiological study

The important radio isotopes used in medicine are shown in the Table.

Transportation

In Great Britain orders must be placed for radioactive isotopes with the Radio Chemical Centre, Amersham but permission for any specific project has to be obtained from the Medical Research Council Conditions and details of ordering, with costs, are given in the Atomic Energy Research Establishment (Harwell) Catalogue, and any isotope labelled compounds can be provided on request. The transportation even of short lived isotopes is possible to-day to any part of the world by special arrangement with the air charter companies. *Beta* emitters need no heavy screen protection but are lead protected, whilst *gamma* emitters are placed in lead containers suspended in the middle of a box or wicker basket so preventing near approach to the active substance. The total amount which can be transported varies from isotope to isotope and depends upon the *gamma*-ray energy

Unit of dosage, detection and measurement

Ionizing radiations have five cardinal properties, penetration absorption effect on a photographic plate, biological action and ionization of solids, liquids

TABLE

Important Radio Isotopes used in Medicine

Element	*Isotope*	*Half life*	*Radiation voltage equivalent* *Beta MeV**	*Gamma MeV*	*End product*	*Medical use*
Phosphorus	^{32}P	14·3 days	1·70 0·69		Sulphur	Blood disorders notably polycythaemia *Beta*-ray therapy
Strontium	^{90}Sr ^{90}Y	21·6 years 60 hrs.	0·53 2·2		Zirconium	

It will be noted that the above are pure beta-ray emitters and thus can be used in the treatment of surface lesions.

Cerium	^{144}Ce ^{144}Pr	282 days 17 mins.	0·3 2·97	0·17 0·135	Neodymium	The gamma-ray activity is of very low energy and can be used in dermatology
Carbon	^{14}C	6,000 years	0·155		Nitrogen	Tracer studies
Bromine	^{82}Br	35 hours	0·447 0·323	1·321 1·036	Krypton	In solution of NaBr for papillomatosis and cancer of the bladder
Iodine	^{131}I	8 days	0·605 0·250	0·637 0·363	Xenon	1. Investigation of thyroid physiology 2. Thyrotoxicosis 3. Tumours of the thyroid
Sodium	^{24}Na	15 hours	1·39	2·76 1·38	Magnesium	Tracer studies on circulation and tissue fluids
Iron	^{59}Fe	47 days	0·46 0·26	1·1 1·3	Cobalt	
Gold	^{198}Au	2·69 days	0·27 0·96	0·411	Mercury	In treatment of malignant effusions
Cobalt	^{60}Co	5·25 years	0·308	1·17 1·33	Nickel	For superficial, interstitial or bomb radiotherapy. The voltage equivalent is up to 3·0 million x-rays

* MeV = million electron volt. An electron volt is a unit of energy used in nuclear physics. It is the kinetic energy of one electron accelerated by falling through a difference of potential of one volt.

and gases through which they pass. They can thus be photographed and measured by electrical methods Photography by their own radiations or autoradiography will give information on the homogeneity and intensity of distribution on a plaque. Localization and concentration of isotopes in living cells which take them up can be demonstrated by laying thin slices of tissue on photographic plates and comparing photographs produced with stained histological sections of the same tissue.

The international unit of measurement is the curie (c) defined as that quantity of any radioactive substance which disintegrates at the rate of $3 \cdot 7 \times 10^{10}$ disintegrations per second This unit is too large and submultiples, millicurie (mc) and microcurie (μc) are used. For x radiation or *gamma* radiation the unit is the röntgen or r unit. For *beta* or any other radiation two other units may be used (*a*) The röntgen equivalent physical (r e.p.), and (*b*) the energy unit. They are defined as that quantity of radiation other than x rays or *gamma* rays which produces an absorption of energy equivalent to 1r of x rays or *gamma* rays. There is also a biological equivalent unit, the röntgen equivalent man (r e m) which is the amount of energy absorbed in tissues which is biologically equivalent to 1r of x rays or *gamma* rays.

Geiger Muller counters

A Geiger counter is a special type of ionization chamber which detects and measures the number of quanta of radiation It can detect the ionization from a single *beta* particle or from electrons from x radiation or *gamma* radiation. It consists of a thin tungsten wire passing down the centre of a brass tube which is filled with argon gas under low pressure. A high voltage is connected between the wire and the case, and there is a high resistance in the circuit This voltage is kept just too low to produce a discharge between the wire and the case, but when the gas is ionized by an electron passing through a discharge will occur An electric current flows, and because of the resistance, the voltage across the counter drops, and so the discharge ceases By placing an amplifier and a loud speaker in the circuit, this change in voltage occurring each time an electron passes through will produce a click A meter may be connected to the amplifier to read the counts per second or they may be recorded on a tape Geiger counters are exceedingly sensitive and can detect even cosmic radiation Although they can be used as rate meters, their main use is to detect radiations. For accurate energy measurements ionization chamber meters are used

Scintillation meters

Light flashes given out when an *alpha* particle or *beta* ray strikes a fluorescent screen can be counted by an electrical mechanism, using a photo multiplier In a scintillation counter the property of fluorescence of certain types of crystals when ionized by electrons passing through them is employed. This fluorescent light activates the photo-sensitive surface of a special vacuum tube with a photo-electric cathode and is known as a photo-multiplier tube Electrons set free at this cathode are accelerated to an anode, with a sensitive surface, and here they produce secondary electrons which are themselves accelerated to a second anode So that ultimately we can obtain amplification a million fold from one electron in the

scintillation crystal. Indeed its main disadvantage is its high sensitivity to "back ground" but by suitable electronic circuits this can be eliminated.

HAZARDS OF RADIOACTIVE ISOTOPES

Hazards from the use of radioactive isotopes are greater than those involved in x-ray or radium therapy. They are (1) externally skin and mucous membrane from *beta* and *gamma* radiation, and (2) internally from entry into the body through the skin, by ingestion or by inhalation, and fixation in the tissues. Special precautions are necessary in their handling, in the decay of radioactive excreta from patients, and in disposal of radioactive waste material into sewage systems. The International Commission on Radiological Protection (1950) has defined the following as maximum permissible doses for workers. (*a*) External radiation Whole body irradiation x-rays or *gamma* rays 0·5 r per week. High energy *beta* rays 1·5 r.e.p. per week. For the hands and forearms only the figures are 1·5 r and 1·5 r.e.p. per week. (*b*) Internal radiation Firm recommendations were not made, but Tables of values for certain isotopes are available.

THE USE OF RADIOACTIVE SODIUM IN CIRCULATION STUDIES

The use of radio isotopes in investigation and in treatment may be illustrated by the following.

A number of tests are available which will give qualitative information about the circulation in any particular area of skin, for example, temperature measurements, reactive hyperaemia. By means of radioactive sodium very accurate measurement is possible of the rate of transfer of sodium ions between the blood and the extra cellular tissue fluids. This provides a quantitative index of the efficiency of the local circulation as far as the supply and removal of diffusible substances is concerned. Baron, Veal and Arnott (1950) have carried out extensive studies on sodium clearance in tube pedicle grafts. They draw a disappearance-rate curve and define a circulation index. If the index is low (4 or 5) local tissue necrosis will occur but a pedicle can be safely divided and transferred with an index of 10 or over. The practical result of this work is that the information obtained about the circulation in such grafts has resulted in a considerable reduction in time and it is now possible to think in terms of weeks instead of months when carrying out these operations.

The experiments can and have been extended to the circulation in the digits and limbs and in the study of vascular diseases of the extremities.

BETA RAY THERAPY

The following remarks apply to P^{32} radioactive phosphorus (half life 14·3 days mean energy 0·69 MeV end product sulphur). Because of the low penetrating power of the rays, the construction of a *beta*-ray plaque so that contamination of the patient with the active substance is avoided is a difficult problem. Radium *beta*-ray plaques are inefficient because unless they are made very fragile the absorption by the monel metal container is very high. Applicators have been made in one of three ways

(1) *Blotting paper soaked in P^{32}* as first used by Low Beer (1950) Our technique is as follows A sheet of blotting paper is marked off into 5 millimetre squares and one drop of P^{32} solution is dropped in the centre of each square. The paper is dried and reloaded and dried twice more. By autoradiography homogeneity is checked After drying, the treatment surface is covered with a thin film of alkathene and the back sealed off with sticky lead acting a triple role of sealing, protection and providing a measure of rigidity The alkathene acts as a water tight gasket so that contamination of the patient will not occur even in moist areas of skin With this applicator a loading of 400 μc per square centimetre gives a dosage rate of 1 000 r per hour on the surface.

(2) Red phosphorus may be incorporated in bakelite as described by Raper and Barnes (1951) This forms a rigid applicator useful for radiobiological work but of limited use clinically

(3) Polythene plastic containing 20 per cent P^{32} as used in the Cancer Hospital London (Sinclair and Blondall 1952). This is flexible and can be cut to any desired shape. The depth dose in the applicators being proportional to thickness the optimum still retaining flexibility is 50 milligrams per centimetre square. If processed by pressure a smooth glossy surface is produced but very slight contamination does occur after prolonged application. Variations in homogeneity may be due to irregular thicknesses in the sheet of plastic, quite as much as to inhomogeneity of the phosphorus, and should always be checked by autoradiography One side of the plastic is cemented to a sheet of lead rubber 2 millimetres thick This backing absorbs 98 per cent of the *beta* particles and acts as a protective covering.

Handling

Measurements and cutting are carried out in a protective metal frame Long handled forceps are used and all work such as cutting applicators to correct shape and size are carried out from the protected surface. Circles are cut with punches and irregular areas by means of a sharp knife after stencilling the shape. Used applicators and unused trimmings or pieces of radioactive material must be allowed to decay to safe low values before being discarded.

Physics

Surface-dose measurements

Surface-dose measurements of the blotting paper applicators have been made on a disc chamber with a front wall of thickness 23 tissue equivalent, that is, 0·023 millimetre or about two cell thickness. It was found to be 1 000 r per hour per 400 microcuries of P^{32} per square centimetre due allowance being made for the absorption by the front wall of the chamber As 4 r will affect a photographic plate, the time for autoradiography can be calculated depending upon the distance between the plate and the film Sinclair and Blondall (1952) using a shallow ionization chamber found the surface dose of their plastic applicators to be in the region of 1 500–2,000 r per hour It will vary with the specific activity of the plastic but 1 23 millicurie per gramme gave an output of 1 000 r per hour

Depth-dose measurements

These are important, for the selection of conditions suitable for *beta* ray therapy will depend upon the penetration Depth-dose curves have been drawn for absorp-

tion in water and with density cardboard phantoms, or other tissue equivalent substances. The half value layer in tissue, that is, the thickness of tissue required to reduce the intensity of radiation to one half is 0·8 millimetre. Fig. 56 shows the depth doses obtained with P^{32} and with a superficial x-ray beam. It can be seen that at 2 millimetres with P^{32} it is of the order of 18 per cent and for superficial x-ray it is 90 per cent. The practical importance of this is that the dose must be accurately specified. A dose of 4 000 r at 1 millimetre may mean 10,000 r on the skin surface. This may be a necrotic dose to a very thin layer but provided it is not too extensive healing will probably occur

Treatment

Low Beer (1950) found that the lowest dose on the skin for a minimal or threshold erythema was 133 r and Sinclair and Blondall (1952) quote 200 r in their particular subject. They further studied skin effects with doses greater than 1,000 r on the skin of the rabbit.

Activity of unimpregnated plastic 970 per hour

	6 days	10 days	28 days
1,000	mild erythema	subsiding	healed
3,000 r	slight erythema	scaly reaction	considerable regression regrowth of coarse hair in one rabbit
5,000	erythema	severe epidermitis but still dry	
7,000 r	erythema only		

Low Beer found that he had to give doses greater than 7 000 r to produce epidermolysis. He has given doses of the order of 17,000 r in 72 hours in the first millimetre of tissue. This has resulted in a severe moist desquamative reaction, but the skin heals in about 50 days. No late skin effects, such as telangiectasia, have been noted up to 5 years later provided the reaction did not exceed a scaly epidermitis.

The author and his colleagues have given doses of the order of 3,500 r in 2–3 hours to areas of up to 12 square centimetres and 5,000 r in two 2,500 r doses on consecutive days to areas up to 100 square centimetres. These produced a severe moist reaction which healed in about 20 days, and a dose of 2,500 r to a 5-centimetre circle in 2 hours produced a mild second degree erythema.

Clinical application

Beta-ray therapy can be used only for very superficial diseases of the skin or mucosae Results in non-malignant conditions such as psoriasis have been equivocal Lesions have responded, only to recur within a short time. Our experience is confined to the treatment of superficial basal-cell carcinoma and intra epidermal carcinoma, and the details of three of our cases will now be given.

Case I A.E.L., aged 59 years

Thirty-five years history of multiple scaly patches on the skin. Affected chest, abdomen, arms, in that order Slow increase in size in last 2 years lesions on abdomen have coalesced and bled. No healing at any time.

Clinical examination (*see* Fig. 56 (*a*) and (*b*)) —Multiple pink scaly patches. Most are flat, with central ulceration. Abdominal area has raised granular hypertrophic edges

(1) Blotting paper soaked in P³² as first used by Low Beer (1950) Our technique is as follows A sheet of blotting paper is marked off into 5 millimetre squares and one drop of P³² solution is dropped in the centre of each square. The paper is dried and reloaded and dried twice more. By autoradiography homogeneity is checked After drying, the treatment surface is covered with a thin film of alkathene and the back sealed off with "sticky lead acting a triple role of sealing, protection and providing a measure of rigidity The alkathene acts as a water tight gasket so that contamination of the patient will not occur even in moist areas of skin. With this applicator a loading of 400 μc per square centimetre gives a dosage rate of 1 000 r per hour on the surface.

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Depth-dose measurements

These are important, for the selection of conditions suitable for beta-ray therapy will depend upon the penetration. Depth-dose curves have been drawn for absorp-

Fig. 58 shows all areas healed 8 months later. Note the excellent cosmetic result in the areas healed with P^{32} but there is residual pigmentation in those areas treated by radium and by x-rays.

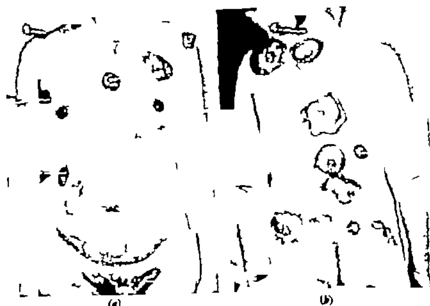


Fig. 57.—Same case as in Fig. 56, 5 months later



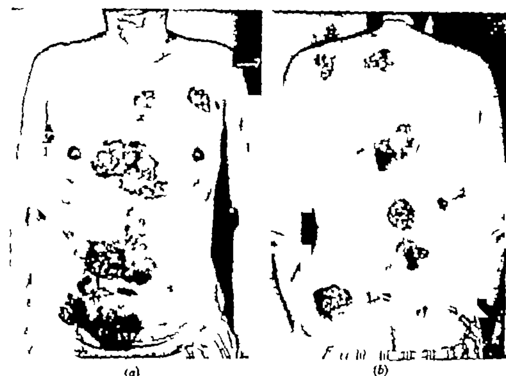
Fig. 58.—Same case as in Fig. 56, showing healing of all areas after 8 months

Case. M.A.B. aged 66 years

Fifty-three years history of psoriasis. Treated over many years with arsenic. 10 years previously epithelioma of back treated by radium. Five years ago and 4 years ago, excision of epithelioma of back and skin graft. Since then further lesions have appeared on the skin of the trunk anteriorly and posteriorly. They start as flat red patches which slowly increase in size, the skin ulcerates, and bleeds and discharges in

Biopsy—Microscopical examination of three lesions on chest and abdomen showed typical basal celled carcinoma W R. and Kahn test negative.

Explanation of photographs—Front and back of patient showing extent and character of lesions before treatment. The two large areas in front were treated with radium on a surface applicator Dose 5 000 r in 7 days at 1 centimetre depth This resulted in a severe moist desquamative reaction which took 6 weeks to heal A lesion on the scalp which was thick, was also treated by means of a surface radium applicator



(*a*) (*b*)

FIG. 56—Basal celled carcinoma

P^{32}	P^{32}	*X-rays*
1 6 000r in 5 days.	9 3 450r in 1 day	A 2,700r in 9 days.
2. 6,000r in 5 days.	10. 3 500r in 1 day	B. 1,500r in 1 day
3 3 500r in 1 day	11 3,500r in 1 day	C 1,500r in 1 day
4 3,500r in 1 day	12. 4 000r in days	D 1,500r in 1 day
5 6,000r in 5 days.	13 4,000r in 2 days.	E. 1,500r in 1 day
6 6,000r in 5 days.	14 3 900r in 1 day	
7 3,900r in 1 day	15 4,000r in 3 days.	*Radium*
8 3,500r in 1 day	16. 3 500r in 1 day	I 5 000r in 8 days.
	17 3 600r in 1 day	II 5 000r in 8 days.

Five small areas on the buttock were healed by superficial x ray therapy (140 kV 5 Ma., 1 mm Al filter)

Four areas accommodated in a 3 centimetres circular field received 1 500 r in a single session A large area needing a 10 10 centimetre field received 2,700 r in 7 fractions over 8 days.

Fig. 57 (*a*) and (*b*), taken 5 months after Fig. 56 (*a*) and (*b*) show the radium-treated area healed and the reactions on the other smaller lesions treated by beta-ray therapy as well as the x ray reactions in the buttocks Doses given are shown in the legend

Fig. 58 shows all areas healed 8 months later. Note the excellent cosmetic result in the areas healed with P^{32} but there is residual pigmentation in those areas treated by radium and by x-rays.

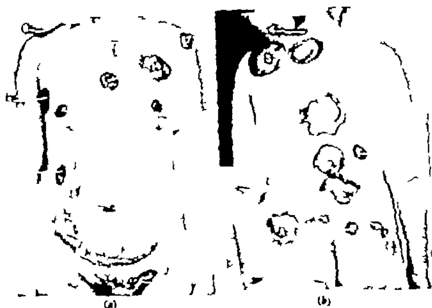


FIG. 57.—Same case as in Fig. 56, 5 months later.

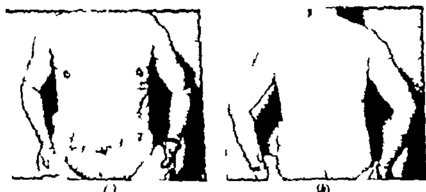


FIG. 58.—Same case as in Fig. 56, showing healing of all areas after 8 months.

Case 2. *M. A. B.*, *aged 66 years*

Fifty-three years history of psoriasis. Treated over many years with arsenic. 10 years previously epithelioma of back treated by radium. Five years ago and 4 years ago, excision of epithelioma of back and skin graft. Since then further lesions have appeared on the skin of the trunk anteriorly and posteriorly. They start as flat red patches which slowly increase in size, the skin ulcerates, and bleeds and discharges in

patches, which are surrounded with scaly scabs The lesions are all very superficial Biopsy Intra-epidermal epithelioma

Treatment *All areas treated with P^{32} beta-ray applicators*

Area	*Field size (cm)*	*Site*	*Dose*	*Time*
1	6·5 4	Back trunk	5,500 r	2 days
2	4 2 3 8	,,	3,500 r	3 hours
3	3 7 2 5		3,500 r	3 hours
4	6·5 4	,,	5,500 r	2 days
5	3 7 2	Right chest	3,500 r	3 hours
6	3 7 2 7	Right leg	3 000 r	3 hours
7	3 5 2	Buttock	3,500 r	3 hours

On the twenty first day area 6 on the right leg had a bleeding moist reaction, the reaction in all other sites being a very brisk erythema with a dry crusting over the whole of each lesion Three weeks later these almost completely healed. The final result shows minimal scarring in all treated sites.

Case 3 I H aged 59 years

Five years history of erythematous patch on right forehead which recently became ulcerated and crusted During the past 12 months red patches have appeared on the temples. On examination on the right temple there is a typical raised rodent ulcer 1 3 1 centimetre Above and below it there are flat scaly erythematous patches. Similar patches on left temple. Histology (1) Basal-cell carcinoma (2) Other lesions show intra-epidermal epithelioma of the basal-cell type

Owing to its thickness the larger lesion (area 1) was treated by superficial x rays, the other lesions (area 2) with *beta*-ray plaques.

Treatment

Area		
1	X-ray 140 kV 5 Ma. 1 mm. Al. filter 2 5 cm. circle at 15 cm F.S D	3,000 r in 1 week
2	Right frontal	2,350 r in 1 2 hours
3	Right lower temple	2,000 r in 1 1 hours
4	Left upper frontal	2,250 r in 1 1 hours
5	Left lower frontal	2,000 r in 1 3 hours

In 14 days they developed a dry erythematous reaction which became crusted on all the lesions. One month later all reactions were healed

CONCLUSION

The advances in x ray engineering and the perfection of Grenz ray and low voltage x ray therapy led to the abandonment of the use of *beta*-ray emitters in dermatology It is only in recent years that their clinical application has become practical in Great Britain, but we are still in the stage of experiment and explora tion concerning their use They seem to promise much in a limited field in dermatology but their use needs a full appreciation of the advantages and limita tions, careful selection of cases, and scientific control Further the cases treated must reach appreciable numbers, and will require to be observed for several years before a full assessment of the work can be made.

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